EXAMINING SURGICAL OUTCOMES FOR THORACIC CANCERS WITHIN A CLINICAL SETTING:

A CLINICAL EPIDEMIOLOGIC PERSPECTIVE

by
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Abstract

Background: Lung and esophageal cancer rank among cancers associated with the highest mortality both in the United States and the World. Surgical intervention provides the best opportunity for cure for these cancers.

Objectives: The objective was to identify factors associated with outcomes in surgical patients with thoracic cancers within a single hospital setting. We sought to achieve this goal with three aims, 1) examine the association between adjuvant chemotherapy and mortality among esophageal adenocarcinoma patients who received combined neoadjuvant chemoradiation therapy followed by surgery, 2) investigate differences by race on recommendation for surgery and survival among early stage non-small cell lung cancer (NSCLC) patients, and 3) determine the effect of HIV infection on post-surgical outcomes among NSCLC patients.

Methods: Data from the Johns Hopkins Hospital Cancer Registry were used for the retrospective cohort study designs and analyses. The Kaplan-Meier method was used to illustrate time to postoperative events. To estimate associations with postoperative mortality we applied Cox proportional hazards regression models. Poisson regression with robust variance was used to estimate the prevalence ratio of surgical recommendation.

Results: *Aim 1:* There was a long-term survival benefit following surgery for patients who received adjuvant chemotherapy compared to no adjuvant chemotherapy (median survival in months: 37.9 vs. 24.7; p=0.057, respectively). Receipt of adjuvant chemotherapy was associated with a 25% decrease in the aHR for postoperative mortality

compared to patients who did not receive adjuvant chemotherapy (0.75; 95% CI 0.55-1.01).

Aim 2: Black patients were 8% less likely to be recommended surgical resection as compared to white patients (crude RR=0.92, 95% CI 0.86-0.98), but this association became null after controlling for patient-, tumor-, and physician-related factors (aRR=0.99, 95% CI 0.93-1.05). There was no significant association between race and mortality (aHR=1.17, 95% CI 0.89-1.55).

Aim 3: The median survival time for HIV-infected cancer patients was significantly shorter than for HIV-unspecified patients (26 vs. 48 months; p=0.001). Mortality among HIV-infected patients was more than threefold that of HIV-unspecified patients (aHR=3.08; 95% CI 1.85-5.13). When additional surgical characteristics were modeled in a matched sub-cohort, the association remained statistically significant (aHR=2.31; 95% CI 1.11-4.81).

Conclusions: Adjuvant chemotherapy for patients with locally advanced esophageal adenocarcinoma was associated with reduced postoperative mortality compared to no adjuvant chemotherapy. Race was not independently associated with surgical recommendation or mortality for early stage NSCLC. After surgery, HIV-infected NSCLC patients have poorer survival than HIV-unspecified NSCLC patients.

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Abbreviations

ACCP	American College of Chest Physicians
ACS	American Cancer Society
aHR	Adjusted hazard ratio
AIDS	Acquired Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
aRR	Adjusted relative risk
ASA	American Society of Anesthesiologists
BAC	Bronchioloalveolar carcinoma
CD4	Cluster of differentiation 4
CI	Confidence interval
CT	Computed tomography
EAC	Esophageal adenocarcinoma
EBV	Epstein-Barr virus
EUS	Esophageal ultrasound
GE	Gastroesophageal
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
HR	Hazard ratio
IQR	Interquartile range
JH	Johns Hopkins
JHSCCC	Johns Hopkins Sidney Comprehensive Cancer Center
KS	Kaposi's sarcoma
NCI	National Cancer Institute
NIH	National Institutes for Health
NHL	Non-Hodgkin lymphoma
NSCLC	Non-small cell lung cancer
PET	Positron Emission Computed Tomography
pCR	Pathologic complete response
pNR	Pathologic no response
pPR	Pathologic partial response
PY	Person-year
RCT	Randomized clinical trial
RR	Relative risk
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized incidence ratio
U.S.	United States
VL	Viral load
ypN0	Postoperative pathologic nodal status absent
ypN1	Postoperative pathologic nodal status present

CHAPTER 1

Background and Literature Review

Introduction

Cancers of the chest, specifically lung and esophagus have a grim prognosis. Even with improved diagnostic and imaging technologies the insidious nature of thoracic cancers often leads to the identification of advanced disease leaving patients and healthcare providers with fewer treatment options. To date, surgical resection of a localized tumor remains the optimal treatment option for a cure [1, 2].

Esophageal carcinoma is the most rapidly increasing solid organ tumor in the western world, and is invariably lethal with an overall 5-year survival of approximately 17% in the 1990s [3]. With current neoadjuvant chemoradiation therapy the 5-year survival rate has almost doubled to 36-40% [4]. A subgroup of patients, about 30%, exhibit complete chemoradiation treatment response with no evidence of tumor in the esophageal specimen after surgery [5, 6]. This small subgroup of complete responders is typically associated with significantly improved 5-year survival of around 70% to 80% [5]. Lung cancer is the second most common and most lethal form of cancer in the U.S. [7]. The 5-year survival after stage I disease drops from 60% to less than 15% for stages II to IV combined [1].

A goal of the research described in this dissertation was to utilize clinical epidemiological methodology to identify factors associated with optimal surgical management and postoperative survival among patients diagnosed with thoracic cancer within a hospital setting. The first study aimed to identify clinicopathologic characteristics associated with post-operative survival following neoadjuvant chemoradiation among esophageal cancer patients. Aim 2 focused on potential racial disparities in the recommendation for surgical intervention as well as postoperative

survival among non-small cell lung cancer (NSCLC) patients. The third and final aims sought to examine differences in postoperative survival and time to recurrence by HIV infection status among NSCLC patients.

Background

Esophageal Cancer

Epidemiology of esophageal carcinoma

Esophageal cancer is the eighth most commonly diagnosed cancer, and the sixth most common cause of cancer death worldwide with a case fatality rate of 90% [7-9] illustrating that cancer of the esophagus remains a highly lethal disease. Developing nations account for more than 80% of the total cases and deaths [10]. Over the past thirty years, esophageal cancer incidence has steadily risen in the U.S.. The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program reports that from 1975-2011 the annual rate of increase in incidence of esophageal cancer was 0.5% [8]. The American Cancer Society (ACS) estimates that in 2014, 18,170 (14,660 in men and 3,510 in women) new cases of esophageal cancer will be diagnosed and approximately 15,450 (12,450 in men and 3,000 in women) patients will die from the disease, in the U.S. [7, 8]. Esophageal cancer is also included among a handful of cancers that are contributing to increasing death rates (20%) among males in the U.S. [11]. Despite these facts, esophageal cancer receives little attention when compared with other cancers such as lung, breast, prostate, and colorectal in terms of health promotion, education and prevention.

Temporal trends in incidence vary for the two major histologic types of esophageal cancer – adenocarcinoma (EAC) and squamous cell carcinoma (SCC) [12, 13] – each apparently having a distinct etiology [14]. Squamous cell carcinoma is the most common histological type worldwide, with a higher incidence in developing countries [15]. The epidemiology of esophageal cancer in the U.S. has dramatically changed over the past thirty years when squamous cell carcinoma was responsible for 90% of the cases. Adenocarcinoma is now the leading histologic type of esophageal cancer in the U.S, representing 80% of incident cases [16]. In 1975 esophageal adenocarcinoma affected four people per million, in 2001 the rate had increased to twenty-three people per million. The National Cancer Institute (NCI) regards esophageal adenocarcinoma as one of the fastest-growing cancers in the U.S. [16]. Incidence rates for adenocarcinoma of the esophagus have been increasing in several Western countries, in part due to increases in known risk factors such as Barrett's esophagus [17], gastroesophageal reflux disease [18], overweight and obesity [19]. In contrast, rates for squamous cell carcinoma have been steadily decreasing in these same Western countries because of long-term reductions in tobacco use and alcohol consumption [19, 20].

In the U.S., the rates and temporal trends of esophageal cancer differ by sex, race, and histologic type. According to a study using SEER data from 1977 to 2005, overall incidence rates for esophageal cancer among men were about triple of those among women. Incidence rates among black men and women (15.8 and 4.7 per 100,000 person-years, respectively) were twice that of white men and women (7.1 and 2.0 per 100,000 person-years, respectively). By histological type, blacks account for 87% of squamous cell carcinoma as compared to only 47% in whites. Black men have the highest incidence

rates for squamous cell carcinoma. The incidence rate for squamous cell carcinoma histology is four times higher in black versus white men (2.7 vs. 13.6 per 100,000 person-years, respectively). Conversely, for adenocarcinoma histology, white males have the highest incidence rates. The rates for adenocarcinoma among white men are five times that among black men and women (3.7 vs. 0.8 and 0.2 per 100,000 person-years, respectively) [21].

Esophageal cancer and survival

Esophageal carcinoma often has an insidious onset and, by the time of diagnosis, most patients are found to have significant nodal metastases with the average patient presenting with advanced stage disease [22]. The overall 5-year survival for disease localized to the esophagus (stage I) was reported to be 34%, while survival for all other stages (stage II-IV) is much lower at 17% [3]. Esophageal cancer treatment and prognosis is based on stage of disease, which is determined by endoscopic ultrasound (EUS) and histologic evalution of a biopsy specimen. Staging of esophageal cancer is categorized by TNM classification which determines how far the tumor has spread into the lining of the esophageus and/or other parts of the body [23]. The American Joint Committee on Cancer (AJCC) [24] recommends the TNM classification system to stratify extent of disease for esophageal cancer into five main categories, stages: 0, I, II, III, and IV (Figure 1-1). Sub-categories further divide each stage for tumor, lymph node, and metastatic involvement. Stage 0 is pre-cancer containing abnormal cells called *high grade dysplasia*, which requires further observation. Stage I is cancer that has grown into the deeper layers of the esophagus wall but has not reached the lymph nodes or other organs. Patients

diagnosed with stage I esophageal cancer are typically those whose cancer was incidently detected early and surgery (esophagectomy) to remove the part of the esophagus that contains the localized tumor is usually sufficient treatment. Stages II includes cancers that have grown into the main muscle layer of the esophagus or into the connective tissue on the outside of the esophagus, and also may include spread to 1 or 2 nearby lymph nodes (stage IIb). Stage III includes cancers that have grown through the wall of the esophagus to the outer layer as well as nearby organs tissues and lymph nodes. Stage IV is the most advanced stage, when the cancer has spread to distant organs and lymph nodes. Patients diagnosed with stages II to IV esophageal cancer are most often recommended chemoradiation followed by surgery [24, 25].

Historically, patients found with locally advanced disease (stages IB to IV) at time of surgery were treated with total or partial esophagectomy and lymph node dissection, and recommended for chemotherapy [26, 27]. Even after this therapy, the five-year survival ranged between 15% and 20% [28, 29]. Survival rates in metastatic esophageal cancer (stage IV) remain low, and outcomes in patients with locoregional (locally advanced, stages IB to IIIB) resectable esophageal cancer have slightly improved since incorporating neoadjuvant chemotherapy and radiation therapy combined with surgery (also referred to as "*multimodality therapy*" and will be used interchangeably throughout this report) in the treatment of this patient population. "Neoadjuvant therapy" is defined as treatment given as a first step to shrink a tumor before the definitive therapy is given, which is almost always surgery (surgery is the definitive treatment for esophageal cancer). Examples of neoadjuvant therapy (also sometimes referred to as *induction therapy*) include chemotherapy, radiation therapy, and hormone therapy, issued

either alone or in combination. Due to encouraging preliminary data in the late 1980s, some high-volume medical institutions began to use combined multimodality therapy in an effort to improve the long-term survival of patients with locally advanced esophageal cancer [2, 30-32].

Therapeutic approaches to treatment and pathologic tumor response for esophageal cancer

Multimodality therapy comprising neoadjuvant chemotherapy and radiation therapy followed by radical resection, or otherwise known as esophagectomy surgery, is increasingly utilized in esophageal cancer and is now an accepted standard of care in the U.S. for patients with locoregional esophageal cancer [33]. A treatment course for a typical patient diagnosed with locally advanced esophageal cancer at Johns Hopkins Hospital is illustrated in Figure 1-2. Although, esophagectomy remains the cornerstone treatment for esophageal cancer [34] the systemic nature, i.e. the high likelihood of microscopic residual disease leading to progression to metastatic esophageal cancer reduces the effectiveness of surgery alone. Numerous observational studies and clinical trials have attempted to address the optimal treatment sequence in managing locoregional esophageal cancer [3, 29, 30, 35-38]. Past data concerning short- and long-term patient outcomes of neoadjuvant chemoradiotherapy plus surgery have been inconclusive with respect to surgery alone. Several randomized trials have shown conflicting results comparing survival between multimodality therapy and surgery alone, but even without definitive data, neoadjuvant chemoradiation has become increasingly more common in clinical practice, especially at high-volume medical institutions, including the Johns

Hopkins Hospital, mainly due to the poor outcome associated with surgery alone [4, 30, 33, 39].

Over the span of 20 years, there have been 10 randomized trials comparing neoadjuvant chemoradiation followed by surgery with other modalities (mainly surgery alone as the control arm) [3, 6, 36, 37, 40-45]. The majority of esophageal cancer patients enrolled in these trials had squamous cell histology, which is less common in the U.S. compared to adenocarcinoma. The most recent trial, published in 2012, was a phase III study (the CROSS study) which randomized patients with locoregional resectable esophageal cancer to receive surgery alone or neoadjuvant chemotherapy with concurrent radiotherapy followed by surgery. Over two-thirds of the patients in this study had adenocarinoma histology. The median overall survival was 49.4 months in the neoadjuvant chemoradiation-surgery group versus 24.0 months in the surgery alone group. The neoadjuvant chemoradiation-surgery group showed a statistically significant reduced hazard ratio (HR) for post-operative mortality compared to the surgery alone group (0.66; 95% CI, 0.49 – 0.87) [6]. The results from this trial has been adopted as the guiding source for current treatment recommendations for patients with locally advanced esophageal cancer. It remains unclear whether survival and response to multimodiality therapy differs by histology, as such, clinical recommendations for therapy do not differ by histology at this time.

The CROSS study reported that 29% of patients who received neoadjuvant chemoradiation followed by surgery achieved a pathological complete response (pCR). A complete pathological response is defined as no evidence of disease found in the resected tumor specimen after administration of preoperative chemotherapy or radiation therapy.

The achievement of a complete pathological response or a major response is associated with an improved survival [32, 35, 46]. The attainment of a complete pathologic response to the neoadjuvant regimen is believed to be the best proxy measure of a successful outcome [47]. Studies have found a pCR can be achieved in 20%-30% of cases with 5-year survival rates of approximately 70% irrespective of the applied treatment protocol, type of histology and tumor stage [5]. However, up to 70% of patients show an incomplete or no response to the neoadjuvant regimen, and the identification of factors that predict a response would be of considerable clinical benefit [47, 48].

Currently, pathological response to mulitmodality therapy is the most informative prognostic marker for patients with locoregional esophageal cancer, regardless of stage or histological type [31, 32]. Analysis based on pathologic stratification not only yields important information about tumor biology but also gives insight into tumor chemo- and radiation sensitivity. Molecular research in understanding how the biology of esophageal tumors respond to therapy is an advancing area. Tumor markers of esophageal cancer are still in development stages of research but could potentially lead to advances in earlier diagnosis as well as playing a key role in assessing tumor response to systemic therapy.

Adjuvant chemotherapy for esophageal cancer

Neoadjuvant chemoradiation followed by esophagectomy remains an essential component of treatment and can lead to improved overall survival compared to surgery alone, especially when performed at high-volume medical institutions. However, the role of adjuvant chemotherapy following multimodality therapy remains unclear. It has been shown that a complete pathological response to multimodality therapy can be achieved in

30% to 40% of esophageal cancer patients with locally advanced disease and has much better 5-year overall survival compared to pathological partial responders and no responders (52% vs. 36% vs. 22%, respectively) [6, 32, 49]. The degree of pathological response remains the most informative predictor of overall and disease-free survival in patients undergoing multimodality therapy. Yet, even among pathological complete responders the postoperative recurrence rate is about 10% to 15% and even higher recurrence rates among pathological partial responders and non-responders (20% to 35%) [32], demonstrating that pathological response is not a perfect predictor of disease-free prognosis. Residual disease among pathological partial- and non-responders and micro-metastases among pathologic complete responders, not identified by current histopathological technology, likely play a role in disease progression and recurrence, respectively.

Only as recently as 2012 was the debate settled on how best to treat esophageal cancer patients with neoadjuvant therapy stemming from evidence from the CROSS study [6]. Adjuvant chemotherapy following multimodality therapy has now become a controversy. To date, there is no standard recommendation of care to guide clinicians on how or when to provide additional chemotherapy after surgery for esophageal cancer patients. No randomized trials have studied efficacy of adjuvant therapy followed by multimodality therapy for esophageal cancer. Reasons against opting to treat patients with adjuvant chemotherapy include chemo-toxicity, patient fatigue, organ insufficiency, co-morbidities, post-operative complications, and mainly lack of data on the long-term clinical benefits or risks to the patient. Arguments for the use of additional chemotherapy following multimodality therapy address the systemic nature of esophageal

cancer and the poor prognosis associated with the disease even among patients that achieve a pathological response to neoadjuvant therapy. Proponents for adjuvant chemotherapy believe that patients who achieved a pathological partial response and are in good physical health after surgery should continue additional chemotherapy to treat their residual disease. Unfortunately, however, evidence supporting the clinical benefits of adjuvant chemotherapy is sparse, inconsistent, and largely anecdotal [32, 33].

Lung Cancer

Epidemiology of lung cancer

Since 1985, lung cancer has been the most common cancer worldwide [50]. Globally, lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death in males and it is the fourth most commonly diagnosed cancer and second to breast cancer in deaths among women. Almost as many Americans die of lung cancer every year as die of prostate, breast, and colorectal cancers combined [51]. In 2008, lung cancer was responsible for 1.6 million (13%) of the total cancer cases and 1.4 million (18%) of cancer deaths, worldwide [52]. Lung cancer is the second most common malignant neoplasm for men and women in the U.S. and is responsible for more deaths than any other cancer [8, 9]. The American Cancer Society estimates for 2014 that about 116,000 and 108,210 new lung cancer cases will be diagnosed for men and women, respectively [7]. In 2014, there will be approximately 159,260 (86,930 in men and 72,330 among women) deaths from lung cancer, accounting for about 27% of all cancer deaths in the U.S. [7]. The 5-year survival rate in the U.S. for lung cancer is dismal (15.6%), and although there has been some improvement in survival during the past few decades, the

survival advances that have been realized in other common malignancies have yet to be achieved in lung cancer.

The majority of lung cancer is diagnosed in older persons with a median age at diagnosis of 71 years in the U.S. [53]. Approximately, 0.2% of lung cancers are diagnosed in patients between age 20 and 34 years; 1.5% (35 to 44 years); 8.8% (45 to 54 years); 20.9% (55 to 64 years); 31.1% (65 to 74 years); 29% (75 to 84 years); and 8.3% (≥85 years) [53].

Lung cancer is a malignancy that arises from the cells of the respiratory epithelium and can be divided into two broad categories. Small cell lung cancer (SCLC) is a highly aggressive malignant tumor derived from cells with neuroendocrine histologic characteristics and accounts for 15% of lung cancer cases. The most common type, non-small cell lung cancer (NSCLC), accounts for the 85% of cases. NSCLC can be further sub-divided into 3 major histologic subtypes- adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma accounts for 40% of all NSCLC cases, with squamous cell carcinoma and large cell accounting for 20% and 2.9%, respectively [54]. Adenocarcinoma has been increasing over the past 30 years and has surpassed squamous cell carcinoma as the most common type of NSCLC. The total (all stages) overall 5-year survival rate for lung cancer in the U.S. for 2001 to 2007 was 15.6%. Patients with localized disease at diagnosis have a 5-year survival rate of 52%; however, the more than 52% of patients with distant metastasis at diagnosis have a 5-year survival rate of only 3.6% [53, 54].

Cigarette smoking is unquestionably the most important preventable cause of lung cancer in the U.S. and worldwide [7]. Cigarette smoking accounts for at least 30% of all

cancer deaths in the U.S. and accounts for 87% and 70% of lung cancer deaths in men and women, respectively [1];with a relative risk of 20 to 25 and an attributable risk of 85% to 90% [55]. Studies have shown reductions in risk for lung cancer after smoking cessation [56]: an 80% to 90% reduction in risk for lung cancer has been seen in smokers who have quit smoking for 10 to 15 years compared to persons who continue to smoke [57]. Other risk factors contributing to the risk of lung cancer include environmental tobacco smoke, occupational exposure to asbestos and radon, and diet [55].

Following the 1964 U.S Surgeon's General Report that evidence was sufficient to conclude that cigarette smoking caused lung cancer, smoking prevalence for males began to decline, followed by women in the 1970's [58]. Since the start of the U.S. lung cancer epidemic in the 1930's, lung cancer has become the leading cause of cancer death in men [1]. The epidemic began in women with a sharp increase in mortality from lung cancer in the late 1960's and has become one of the top two leading causes of death among women in the U.S [1, 59]. Although mortality rates of lung cancer for men began to decline in the 1980's, women are only now beginning to show a slight decline in lung cancer mortality [1, 7]. The incidence and mortality rates for lung cancer tend to mirror one another because most patients diagnosed with lung cancer eventually die of it. In men in the U.S., lung cancer death rates have decreased by 2% per year from 1994 to 2006 [51]. However, during the same period (1995 to 2005), lung cancer death rates in women continued to increase by 0.3% per year [51]. Far more men than women still die from lung cancer each year, but the gender gap in deaths from lung cancer is steadily narrowing [51]. This trend is due to historical differences in smoking patterns, with smoking prevalence having peaked approximately 20 years earlier among men than women [58, 60].

Among cigarette smokers, the incidence of lung cancer is higher among blacks and Native Hawaiians and other Polynesians and lower among Japanese Americans and Hispanics compared to whites in the U.S. [61]. However, racial and ethnic differences seem to dissipate among individuals with heavy smoking (>30 cigarettes per day). Thus racial and ethnic differences in lung cancer rates have been initially attributed to variations in cigarette smoking patterns. Smoking prevalence in the U.S. is lowest among Asians (9.9%) and Hispanics (15.8%) and highest among American Indians and Alaska Natives (32.4%), whereas blacks and whites have similar rates 21.3% and 22%, respectively [62] even after adjusting for age [50]. However, only 8% of black smokers smoked at least 25 cigarettes per day compared to 28% of white smokers in the U.S. [62]. Nevertheless, differences in lung cancer rates by race remain. Black men are about 40% more likely to develop lung cancer than white men [62, 63]. The incidence rate is similar in black and white women and women also have lower rates than men but the gender gap has been closing [8, 64, 65].

Disparities in surgical therapy for lung cancer

Although cigarette smoking has declined significantly over the past 50 years, disparities in tobacco use remain across groups by race, ethnicity, educational level, and socioeconomic status and also across regions of the U.S. Major advances have been made in the ability to image and identify lung tumors and metastases, diagnose and stage lung cancer with minimally invasive techniques, and safely resect early-stage lung cancers in patients. Despite such advances disparities in treatment and survival remain. A disproportionate number of cancer deaths occur among racial and ethnic minorities,

particularly African Americans, who have a 33% higher risk of dying of cancer than whites [66]. Although differences in incidence and stage of disease at diagnosis may contribute to racial disparities in mortality, inequalities in the receipt of cancer treatment may play an important role. Poor screening and prevention efforts, health care system and provider biases, and differences in patient socioeconomic and socio-cultural characteristics are thought to be prevailing factors underlying racial disparities.

A study using SEER data from 1988 through 1995 reported that among patients diagnosed with NSCLC, black patients less frequently received a recommendation for surgery than white patients [67]. Similarly, an analysis of Medicare data from 1985 through 1989 showed lower surgical resection rates for local/regional stage non-small cell lung cancer and higher rates of no definitive treatment of distant-stage non-small cell lung cancer among black patients compared to white patients [68]. Pulmonary resection provides the best chance of cure for patients with early-stage disease [69-71]. Black patients with early-stage lung cancer have lower 5-year survival rates than white patients, and this difference in outcome has been attributed to lower rates of resection among black patients [64].

In a prospective study by Cykert et al, [72] the surgical resection rates for patients with tissue-confirmed non-small cell lung cancer of equal stage at diagnosis were 63% for blacks vs. 75% for whites, which was statistically significant ($p=0.03$). In a retrospective study using SEER data between 1985 and 1993, Bach et al, [71] also reported that blacks were significantly less likely to undergo surgical resection than whites for non-small cell lung cancer (64.0% vs. 76.7%; $p<0.001$, respectively). In addition, the 5-year survival was significantly lower for blacks, a finding associated with

the difference in resection rates [64, 71]. It has been shown that surgical treatment can [71] improve survival across race groups. Farjah et al, [73] found a difference in rate for surgical treatment between blacks and whites, however among those who did undergo surgery, blacks and whites postoperative survival were similar. Disparities in lung cancer care also have been found in other groups. Hispanic patients with stage I non-small cell lung cancer have lower rates of surgical resection and poorer survival as compared with white patients [74].

Barriers to the receipt of optimal cancer therapy are likely numerous and complex [75]. Several potential factors underlying racial differences in the receipt of surgical therapy include differences in pulmonary function [76], access to care [77], refusal of surgery [78], beliefs about tumor spread on air exposure at the time of operation [79] and the possibility of cure without surgery [80], distrust of the health care system and physicians [81], suboptimal patterns of patient and physician communication [82], and health care system and provider biases [73, 83, 84]. Differences in patient characteristics (i.e., lung function, performance status, and severity of comorbidities) and health care system and provider biases are often argued to be significant factors underlying racial disparities [72, 85].

Epidemiology of HIV-associated non-small cell lung cancer

A number of epidemiologic studies have noted an elevated risk of lung cancer among HIV-infected individuals [86-93]. Since the introduction of highly active antiretroviral therapy (HAART), persons infected with human immunodeficiency virus (HIV) have been living longer, healthier lives [94]. Concomitantly, there has been a

decrease in AIDS-related malignancies such as Hodgkin lymphoma and Kaposi sarcoma [95] and an increase in the proportion of deaths attributable to non-AIDS-defining tumors, especially lung cancer [96, 97]. However, their risk of developing lung cancer seems to be much higher than that in the general population even after controlling for elevated rates of cigarette smoking in the HIV-infected population [98-101]. Lung cancer is the third most frequent cancer in persons with HIV infection, only after AIDS-defining malignancies of Kaposi sarcoma and non-Hodgkin lymphoma [88, 102]. In fact, lung cancer is the most common and most deadly non-AIDS-associated cancer in the HIV-infected population, accounting for 16% of deaths in patients with HIV infection [103].

While the higher risk of lung cancer in HIV-infected population compared to the general population of the same age seems to be due, in part, to the higher prevalence of smoking among HIV-infected patients, smoking does not appear to explain all of the excess risk with relative risks ranging between 2.0 and 4.0 after adjustment for smoking [99, 100]. Although smoking remains an important risk factor for the risk of lung cancer among HIV-infected persons, several other factors may contribute to the higher incidence. These include greater prevalence of co-infection with oncogenic viruses, such as human herpesvirus 8, human papillomavirus and Epstein-Barr virus. HIV-infected populations also have a higher prevalence of comorbidities that are associated with higher risk for lung cancer, including pneumonia and tuberculosis, which induce prolonged inflammation processes. Direct consequences of HIV could also play a potential role in the development of lung cancer such as long-term immunosuppression [104].

Surgical intervention for HIV-infected non-small cell lung cancer

Typically, HIV-infected lung cancer patients present at a younger age, with more advanced stage of disease, and worse overall survival as compared to the general population [105, 106]. In fact, so advanced is the stage at presentation, that only 10-15% of HIV lung cancer patients have disease amenable to curative resection [106]. The median survival of lung cancer patients with HIV infection is only 3 to 6 months as compared to all patients with advanced staged lung cancer (10 to 12 months) [106-111]. The poor performance status of patients with HIV infection and lung cancer undermines their ability to tolerate surgery, chemotherapy, and radiation therapy [112]. HIV-infected lung cancer patients with in good general health, with higher CD4 counts and adherent to highly active antiretroviral therapy should have a survival advantage after cancer treatment [113, 114].

No single institution has accumulated a large experience with these patients, and to date, little is known about the clinical efficacy of surgical resection, when appropriate, in HIV-infected lung cancer patients. Due to the small number of patients presenting with early disease, only a few authors have reported on surgical outcomes in this patient population using very small numbers of case reports [96, 109, 112-119] with a cumulative total in the literature of fewer than twenty-five HIV-infected lung cancer patients who have undergone surgical resection. At present, the general consensus based on this limited set of cases has been for aggressive surgical resection in HIV-infected patients with localized disease and good performance status [112, 114].

Significance

The purpose of the studies featured in this dissertation was to apply a clinical epidemiological approach to examine key factors that play an important role in the treatment and survival of patients diagnosed with thoracic cancers. The Johns Hopkins Hospital Cancer Registry is the source population from which inferences are made on the target population, i.e., *thoracic cancer patients treated in a hospital setting*. Our conclusions based on adjuvant chemotherapy for patients diagnosed with locally advanced esophageal adenocarcinoma who received multimodality therapy will provide clinicians with information to make better treatment decisions. We expect that our work will further understanding of the complex relationship between disparities in race and surgical treatment and survival among early stage NSCLC patients and provide additional clinical insight on why candidates for surgery may refuse treatment. Finally, our results based on HIV-infected NSCLC patients who undergo surgery for curative intent will inform medical and public health collaborative programs on recommendations for best treatment practices for the unique set of challenges posed by this group of NSCLC patients. Ultimately, we hope our work provides future guidance in medical practice and further promotes clinical and public health research for lung and esophageal cancers.

Specific Aims

The specific aims and associated hypotheses of this dissertation are as follows:

Aim 1. To examine the association between adjuvant therapy and postoperative mortality among locally advanced esophageal adenocarcinoma patients treated with combined neoadjuvant chemoradiation followed by surgery.

Using data from the Johns Hopkins Hospital Cancer Registry between 1989 and 2011, we investigated the association between clinicopathologic prognostic characteristics of patients treated with and without adjuvant chemotherapy and time from surgery to death accounting for pathologic response to neoadjuvant therapy.

We hypothesized that patients diagnosed with locally advanced esophageal adenocarcinoma who received adjuvant chemotherapy would have improved survival compared to patients with similar clinicopathologic characteristics and pathologic response who received combined chemoradiation followed by surgery alone treated at Johns Hopkins Hospital between 1989 and 2011.

Aim 2. To investigate differences by race on recommendation for surgical therapy and postoperative survival among early stage non-small cell lung cancer patients.

To better understand the relationship between race and recommendation for surgery, we conducted a retrospective cohort study using the Johns Hopkins Hospital Cancer Registry of patients enrolled from 2000 to 2010.

We hypothesized that there would be no racial disparities among patients with early-stage non-small cell lung cancer patients who received a recommendation for

surgery at Johns Hopkins Hospital between 2000 and 2010 after accounting for other patient-, tumor- and physician-related factors. We further hypothesized that overall survival would not differ by race once surgical recommendation was taken into account.

Aim 3. To determine the effect of HIV infection on post-surgical outcomes among non-small cell lung cancer patients.

Utilizing data from the Johns Hopkins Hospital Cancer Registry, we examined differences in clinical characteristics and all-cause, cancer-specific, and progression-free survival between HIV-infected and HIV-unspecified NSCLC patients who underwent surgery at Johns Hopkins Hospital from 1985 to 2010. A matched subcohort analysis further examined detailed intra- and post-operative differences between HIV-infected and HIV-unspecified NSCLC surgical patients.

We hypothesized that HIV-infected patients with NSCLC would have poorer postoperative survival compared to HIV-unspecified NSCLC patients with similar clinical risk factors who underwent surgery at Johns Hopkins Hospital from 1985 to 2009. We further hypothesized that HIV-infected patients would have shorter time to disease progression as compared to HIV-unspecified patients with similar clinical risk factors following surgery with curative intent.

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Figure 1-1. Stages of Esophageal Carcinoma

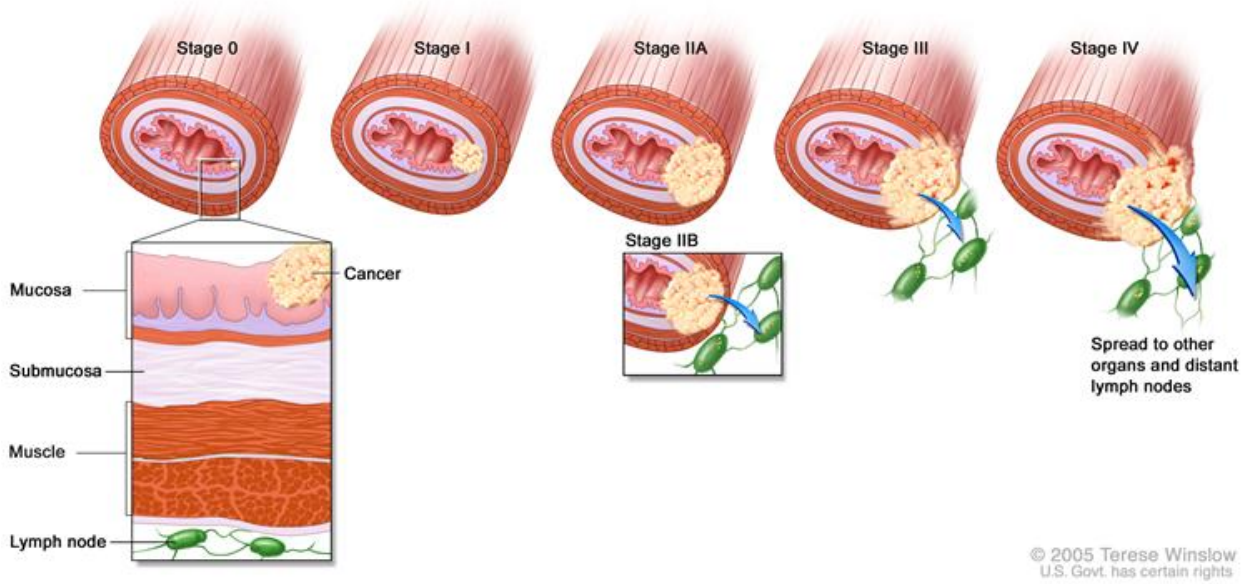
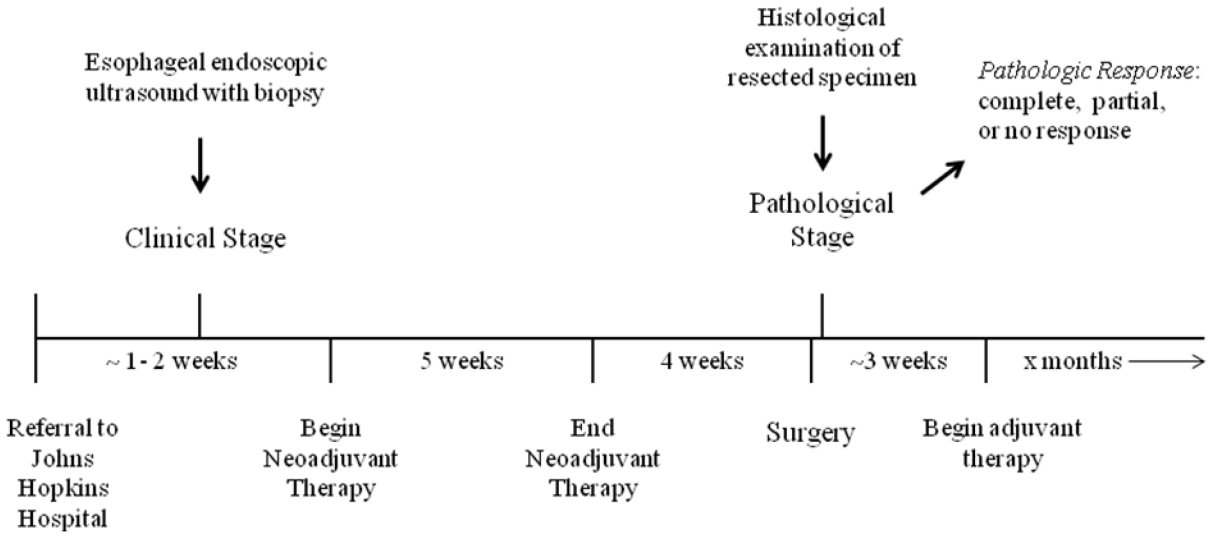


Figure 1-2

Figure 1-2. Treatment Course for Typical Locally Advanced Esophageal Cancer Patient At Johns Hopkins Hospital



CHAPTER 2

Pathologic Response to Neoadjuvant Therapy May Inform Treatment Decisions for Adjuvant Chemotherapy for Esophageal Adenocarcinoma

Pathologic Response to Neoadjuvant Therapy May Inform Treatment Decisions for Adjuvant Chemotherapy for Esophageal Adenocarcinoma

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Abstract

Background: Evidence informing current guidelines advising adjuvant chemotherapy subsequent to neoadjuvant chemoradiation therapy followed by surgery, also referred to as *multimodality therapy,* for esophageal cancer is limited. Our objective was to identify patients with locally advanced esophageal adenocarcinoma treated with multimodality therapy that may benefit from adjuvant chemotherapy.

Methods: A single institution retrospective cohort study was performed in 308 patients with esophageal adenocarcinoma who underwent multimodality therapy between 1989 and 2011. Kaplan-Meier analysis compared postoperative survival by clinical response to multimodality therapy and the use of adjuvant chemotherapy. Cox proportional hazards regression models estimated the association of adjuvant chemotherapy with postoperative mortality.

Results: After multimodality treatment, 30% (93/308) received adjuvant chemotherapy. Partial response to multimodality treatment was observed in 150 (48%) patients; 50 of whom received adjuvant therapy. The median survival for partial responders who received adjuvant therapy vs. those receiving multimodality therapy alone was 53.2 vs. 27.6 months, respectively (p=0.047). Patients with complete response or no response to multimodality therapy showed no difference in median survival with the addition of adjuvant chemotherapy. Cox regression revealed a 25% decrease in relative hazard for long-term survival amongst patients who received adjuvant chemotherapy compared to no adjuvant therapy after adjusting for clinical response to multimodality therapy, age, and ASA score (aHR=0.75, 95% CI 0.55-1.01).

Conclusions: Adjuvant therapy for patients with locally advanced esophageal adenocarcinoma was associated with decrease in postoperative mortality compared to multimodality treatment alone, after adjusting for clinical response, age, and ASA. Partial responders may benefit most from adjuvant chemotherapy.

Introduction

In the United States (U.S.), there was an estimated 17,990 new diagnoses of esophageal carcinomas and 15,210 deaths in 2013 [1]. Historically, before the advent of modern surgical, chemotherapeutic or radiotherapy modalities, mortality associated with esophageal carcinomas in the U.S. has been high, with an estimated overall survival of 5% between 1975 and 1977. When surgical resection alone became the standard of care, cure rates improved in the range of 10-20% [2]. Nevertheless, the high rates of local and distant failure prompted increasingly aggressive perioperative treatments. While multiple clinical trials have individually demonstrated the efficacy of neoadjuvant therapies on patient survival, the optimal sequence of perioperative treatment remains to be elucidated.

In the current era of multidisciplinary treatment options, perioperative strategies have been estimated to improve survival for esophageal carcinoma by approximately 15% compared to surgery alone [3]. A meta-analysis by Sjoquist which included 9 randomized trials found a 13% decreased risk of all-cause mortality amongst patients with esophageal and gastroesophageal (GE) junction cancers who received preoperative chemotherapy vs. surgery alone (HR 0.87; 95% CI, 0.79-0.96, $p<0.005$) [4]. Notably, the CROSS Trial revealed that pre-operative carboplatin and paclitaxel in combination with radiotherapy improved overall survival (HR 0.657, $p=0.003$) [5].

At our institution, preoperative chemoradiotherapy became a treatment option for patients with esophageal carcinoma as early as 1989, and subsequently became the backbone element of perioperative, multimodality therapy. Importantly, adjuvant chemotherapy was never embraced. This was partly due to its poor tolerability by patients

after multimodality therapy, its theoretical disadvantages including postoperative removal of blood supply, and poor compliance with medication. Overall, there was no convincing evidence of the direction of the effect of adjuvant therapy after resected esophageal cancer.

Trials that have focused on adjuvant therapy have offered a mixed view. For resected gastroesophageal(GE) junction and gastric cancers, there is some evidence suggesting a slight benefit from the American Intergroup 116 trial in 2000, in which patients who received adjuvant chemoradiation with bolus 5-fluorouracil(FU)/ leucovorin had an increased relapse-free survival (RFS) and overall survival (OS) vs. observation alone (3-year OS 51% vs. 40%, p=0.005) [6]. The Japanese Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer study, using a mixture of tegafur, gimeracil and oteracil, found a significant improvement in RFS and OS (3-year OS 80.1% vs. 70.1%, p=0.003) [7]. In Europe, results from the phase III Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial found that patients with gastric cancer who received 3 cycles each of pre- and postoperative ECF (epirubicin/cisplatin/infusional 5-FU) and surgery resulted in significant increased 5-year OS compared to surgery alone (36% vs. 23%, p=0.009) [8]. There is unfortunately however, a paucity of data focusing on outcomes following adjuvant chemotherapy after multimodality therapy for esophageal cancers.

Since there is so little evidence informing current guidelines advising on whether to use postoperative chemotherapy following multimodality therapy for esophageal adenocarcinoma, the 2013 National Comprehensive Cancer Network (NCCN) guidelines for adenocarcinoma only states that preoperative chemoradiation is the preferred primary

treatment for patients with resectable tumors (T1b, N+ and T2-T4a, N0-N+) and are medically fit for surgery [9]. All postoperative treatments recommendations are based on surgical margins. Our objective was to assess the long-term survival of patients with locally advanced esophageal adenocarcinoma treated with multimodality therapy and adjuvant chemotherapy. We hypothesized that patients who received adjuvant chemotherapy would have improved survival compared to patients with similar clinicopathologic characteristics who received multimodality therapy alone.

Methods

Study population

The study cohort was comprised of patients with biopsy-proven esophageal adenocarcinoma and a documented assessment by a thoracic surgeon, medical oncologist, gastroenterologist, and radiation oncologist at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins Hospital (JHH) between May 1, 1989 and August 31, 2011 from the JHH Cancer Registry. Patients were included if they underwent multimodality therapy, which was defined as receiving pretreatment clinical staging, neoadjuvant chemotherapy and radiotherapy and an esophagectomy with curative intent.

The JHH Cancer Registry collects data on all patients diagnosed with and/or treated for all cancers, including esophageal cancer, at JHH. Following national standards for data collection, coding, and staging, JHH certified tumor registrars collect data on incidences, primary site, histology, extent of disease, treatment, and outcomes. The JHH

Cancer Registry assures lifetime follow-up of cancer patients and assures that 96% have current information within the last 14 months.

Data collection

Data were collected from the JHH Cancer Registry, and additional clinical data were abstracted from hospital records, electronic and paper files. Vital status was determined through December 31, 2012. In addition, to the JHH Cancer Registry's active surveillance for vital status; patients who were identified as not being deceased by the JHH Cancer Registry were cross-validated using surgeons' case logs and the Social Security Death Index. The Johns Hopkins University School of Medicine Institutional Review Board approved this study.

Clinical Variables

Clinical variables included: smoking history, tumor site, neoadjuvant chemotherapy and radiation regimens, surgical procedure, ASA status, post-operative complications, clinical and pathological staging, and adjuvant chemotherapy regimens. Smoking history was self-reported as the number of packs smoked per day and total number of years smoked. Smoking status was categorized into no history or ever history of smoking. Tumor site was anatomically classified as the upper, middle, or lower third of the esophagus or the gastro-esophageal junction based on imaging and intra-operative findings. The American Society of Anesthesiologists 5-grade classification system was used as an index of preoperative comorbidities [10]. Post-operative complications were extracted from medical records, and patients were ultimately categorized as having any or

no post-operative complications. Pre-operative clinical staging was determined with the combinations of endoscopic ultrasound (EUS) first used in 1995, computed tomography, and positron emission tomography (PET) first used in 2000. Pathological stage was determined using the pathology record. Pathologic response to neoadjuvant chemoradiation was determined at the time of pathologic examination of the surgical specimen.

Pathologic response to neoadjuvant therapy was classified as complete response (pCR), partial response (pPR) and non-response (pNR). A patient was considered to have a complete pathologic response if no microscopic evidence of tumor was found upon examination of both the resected esophageal specimen and nodal tissues (T0N0M0). Partial response was defined as persistence of microscopic esophageal carcinoma in the resected surgical specimen but the pathological stage according to the American Joint Committee on Cancer (AJCC) was lower compared with the preoperative clinical stage. Non-response was defined as patients with no change in AJCC stage between clinical and pathologic staging, or progression of disease despite neoadjuvant therapy.

Chemotherapy regimens

To investigate whether the type of adjuvant chemotherapy administered would deliver different outcomes, every patient's perioperative chemotherapy course was classified as being the same or different. All 93 patients who received adjuvant therapy had known perioperative regimens. Neoadjuvant and adjuvant chemotherapy regimens were documented as the agents used prior to and following surgery, respectively. Each agent was classified under its primary mechanism of action. These included

antimetabolites, platinum-containing alkylating agents, taxanes, topoisomerase I and II inhibitors, EGFR inhibitors, VEGF inhibitors, and cytotoxic antibiotics. A patient's adjuvant chemotherapy regimen was defined as being *different* from their neoadjuvant chemotherapy regimen if there was a minimum of one adjuvant agent with a different mechanism of action from any neoadjuvant agent.

Statistical Analysis

Comparison of continuous, dichotomous, and categorical variables was performed using the nonparametric Wilcoxon rank sum test and x^2 test for homogeneity, respectively. Time to all-cause mortality was examined using the Kaplan-Meier method, and survival differences were compared using the log rank test. Overall survival was defined as elapsed time from surgery date to death or the latest follow-up.

A Cox proportional hazards regression model was constructed to determine the association between adjuvant therapy and mortality. The model was adjusted by risk factors that included pathological response, age at diagnosis, and ASA performance status. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. Test based Schoenfeld residuals were used to confirm the proportional hazards assumption for the multivariable Cox regression model. All statistical tests were two-sided and results were considered statistically significant for p values ≤ 0.05. All analyses were performed using STATA statistical software, v10.0 (StataCorp LP, College Station, Texas).

Results

Baseline Characteristics

Between June 1989 and July 2011, 308 patients underwent multimodality treatment for esophageal adenocarcinoma at our institution, of whom 93 (30%) received adjuvant chemotherapy. Clinicopathologic characteristics of the study population according to receipt of adjuvant chemotherapy are displayed in Table 2-1. Overall, the study consisted of mostly white men. Patients receiving adjuvant therapy were younger (median age, 57 versus 62; p=0.023) and smoked fewer pack years (median pack years, 26 versus 32; p=0.025), compared to patients who did not receive adjuvant therapy. There was no difference between median ASA scores between the two groups. Tumor was located in the lower third of the esophagus in 61% of patients. The majority of patients were clinically staged by PET with EUS; 81% within the adjuvant group and 78% within the no adjuvant group. Patients who did not receive adjuvant therapy experienced a slightly longer time interval between diagnosis and surgery by 6 days compared to those who did receive adjuvant chemotherapy. The surgical approach to esophageal resection was a transhiatal approach in the majority of patients; 85% and 83% in the adjuvant and no adjuvant groups, respectively. Patients who did not receive adjuvant therapy had a slightly increased median length of hospital stay by one day. Post-operatively, there was no significant difference between the proportions of patients who experienced complications following esophagectomy.

Clinical and Pathological Staging

The distribution of clinical and pathological stages according to receipt of adjuvant chemotherapy is presented in Table 2-2. The majority of patients presented initially at clinical stage cIII, without significant difference between the groups. Pathologically, the majority of patients in both groups were stage ypIIA, followed by those having no residual disease. Similar percentages of patients in both groups were complete responders, partial responders, and non-responders to neoadjuvant chemotherapy (p=0.393).

Outcomes and survival

Using Kaplan-Meier estimates, there was a marginally statistically significant higher long-term survival following surgery for patients who received adjuvant chemotherapy. Median overall survival was 37.9 months for patients who received adjuvant chemotherapy and 24.7 months for patients who did not (p=0.057) (Figure 2-1). Stratified by clinical response, partial responders who received adjuvant therapy lived a median of 26 months longer than those who received multimodality therapy alone (Figure 2-2). The median survival after adjuvant vs. no adjuvant therapy between complete responders or those who showed no response to neoadjuvant therapy was not statistically different (Figure 2-2).

Multivariable-adjusted hazard ratios were calculated to assess the association between adjuvant therapy and mortality, adjusting for clinical response, age at diagnosis, and ASA performance status (Table 2-3). Receipt of adjuvant chemotherapy was associated with a 25% decrease in relative hazards for postoperative mortality compared

to patients who did not receive adjuvant chemotherapy, which approached statistical significance (aHR=0.75; 95% CI 0.55 – 1.01; p=0.065).

Comparing adjuvant regimens

The median number of adjuvant chemotherapy cycles received was 3 cycles. Median ECOG performance status was 0.5. There were a total of 14 Grade 3 and 5 Grade 4 adverse events (Table 2-4). The most commonly delivered neoadjuvant chemotherapy regimen was cisplatin and 5-flurouracil. The most commonly delivered different adjuvant chemotherapy regimen was the addition of a taxol.

Forty-nine (53%) received the same regimen while the remaining 44 (47%) received different regimens. Among complete responders (20/93), there was no difference in proportion by who received the same or different regimens (50% same vs. 50% different). A larger percentage received the same regimen within the partial responders group (50/93) (58% same vs. 42% different) while a larger percentagereceived a different regimen among those who did not respond to neoadjuvant therapy (23/90) (56% different vs. 43% same; p=0.495).

The comparison of median survival between patients receiving same or different adjuvant chemotherapy regimens stratified by clinical response is displayed in Table 2-5. There did not appear to be a difference in median survival for same vs. different chemotherapy regimens for complete, partial, or non-responders. Amongst partial responders, patients were further stratified by pathological nodal status into node negative or node positive (Table 2-5). Median survival was not yet reached for those with negative nodes who received the same adjuvant treatment. A longer median survival was observed

for patients with positive nodes who received different regimens compared to those who received the same regimen (53 vs. 18 months), though this difference was not statistically significant. Using Kaplan-Meier estimates, pathological node-negative partial responders who received the same adjuvant regimen appeared to have greater long-term survival compared to those who received a different regimen (Figure 2-3). Meanwhile, node-positive partial responders appeared to have greater median survival if they received a different adjuvant regimen, however this difference was not found to be statistically significant (p=0.217).

Discussion

This was a retrospective analysis of over 20 years experience at our institution of patients treated with multimodality therapy for esophageal adenocarcinoma. We found that partial responders to multimodality therapy who received adjuvant therapy lived a median of 26 months longer than those who received multimodality therapy alone. Partial responders have distinct survival trajectories between recipients of adjuvant vs. no adjuvant therapy as early as one year post-operatively that persists up to ten years. Moreover, our data suggest that once you give a neoadjuvant chemotherapy regimen that provokes a response, more of that same chemotherapy given adjuvantly may improve survival benefit. For instance, we observed that partial responders, who responded so well to a certain neoadjuvant chemotherapy regimen that pathologically there was no evidence of malignancy in previously positive regional lymph nodes, demonstrated by a survival advantage when the same chemotherapy regimen was used adjuvantly. A plausible

explanation would be that the original tumor was sensitive to the initial regimen, and any remaining microscopic disease following surgical resection would similarly display susceptibility to the same regimen. Of note, tests for interaction between mortality and pathologic response to multimodality therapy were not statistically significant. However, the authors decided that sub-group analyses were clinically relevant.

When partial responders did not respond well enough to pathologically clear their regional lymph nodes after the initial, neoadjuvant chemotherapy, changing the chemotherapy regimen in the adjuvant setting showed a trend towards longer survival. This implies that malignant cells that were resistant to the initial regimen were specifically targeted by a different molecular mechanism. Although these results were not statistically significant, likely due to the small sample size of pathologic responders, they prompt the need for additional research on the effects of changing chemotherapy regimens following initial response. This rationale for using the same or different chemotherapeutic regimens both before and after surgery would be even better implemented as new molecular markers of chemosensitivity are brought to the clinic.

Based on Kaplan-Meier analysis, complete responders have the greatest long-term survival, with indistinguishable survival curves between those receiving adjuvant vs. no adjuvant. This may be expected, as patients with no residual disease would have no additional targets for adjuvant chemotherapy. Similarly, there does not appear to be a survival difference amongst patients who demonstrated no response to neoadjuvant therapy. The tumor biology that prevented resistance to initial therapy may explain why additional chemotherapy of the same mechanism provided no advantage. It is arguable

that patients who showed no response based on pathological staging may benefit from a different chemotherapy regimen postoperatively or alternative therapies where available.

While encouraging, the results of this study are limited by the retrospective methodology. Additionally, the side effects of perioperative chemoradiotherapy and its impact on patient quality of life and satisfaction were not considered. There may have been preferential selection for patients to undergo adjuvant chemotherapy given knowledge of clinical response to multimodality therapy. However, the distributions for receiving adjuvant therapy by clinical response was not statistically significantly different ($p=0.393$). It is also possible that the mechanism for decision to undergo adjuvant therapy may be more strongly related to patient health than pathologic complete response. Unfortunately, patient's decision and reasons to accept or decline adjuvant therapy were not available. Finally, patients may have been enrolled in strict study protocols that precluded the option for adjuvant therapy or deviation from a chemotherapy regimen.

Conclusions

From our study, we conclude that adjuvant chemotherapy is advantageous in the multimodality approach for select patients with locally advanced esophageal adenocarcinoma. We found that outcomes following adjuvant therapy were dependent on clinical response to multimodality therapy. Specifically, partial responders were found to have longer overall median survival with adjuvant therapy vs. multimodality therapy alone. The results of this study may aid clinicians in deciding whether a patient with complete, partial, or no response to multimodality should receive additional adjuvant chemotherapy. Additionally, our preliminary results prompt the need for further

investigations into the possible advantages of altering adjuvant chemotherapy regimens based on the initial response to adjuvant chemotherapy as well as pathologic nodal status.

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Table 2-1: Study Characteristics According to Adjuvant Chemotherapy vs. No Adjuvant Chemotherapy (N=308).

	Adjuvant Treatment 93 (30.2%)		No Adjuvant Treatment 215 (69.8%)		
	#	%	#	%	p value
Median age at Diagnosis, years (IQR)	57	(52 - 64)	62	(51 - 69)	0.023
Sex					
Male	86	92.5	202	94.0	0.628
Female	7	7.5	13	6.0	
Race					
White	90	96.8	208	96.7	0.989
Non-white	3	3.2	7	3.3	
Smoked Cigarettes					
Never	16	17.2	39	18.1	0.844
Ever	77	82.8	176	81.9	
Pack-Years Smoked, median years (IQR)	26	(15 - 38)	32	(20 - 50)	0.025
ASA					
2	9	9.7	31	14.4	0.547
3	81	87.1	173	80.5	
4	3	3.2	9	4.2	
5	0	0.0	2	0.9	
Tumor Site					
Upper Third	0	0	1	0.50	0.419
Middle Third	6	6.5	8	3.7	
Lower Third	57	61.2	131	60.9	
Distal	0	0.0	6	2.8	
GE junction/Cardia	30	32.3	69	32.1	
Diagnostic Modality					
CT only	1	1.1	31	14.4	<0.001
CT/EUS	17	18.3	17	7.9	
PET/EUS	75	80.6	167	77.7	
Year of diagnosis					
1988-1989	0	0	2	0.9	0.634
1990-1999	29	31.2	75	34.9	
2000-2011	64	68.8	138	64.2	
Median days between diagnosis and surgery	111	(97-126)	117	(104-136)	0.035
Transhiatal surgical approach	79	85%	179	83%	0.216
Median length of hospital stay, days (IQR)	8	8-9	9	8-13	<0.001
Post-operative complications	35	37.6	99	46.1	0.351

IQR, interquartile range; ASA, American Society of Anesthesiologists; GE, gastroesophageal; CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography

Table 2-2: Distribution of Clinical and Pathological Stages of Patients Receiving Adjuvant Chemotherapy vs. No Adjuvant Chemotherapy.

	Adjuvant Treatment 93 (30.2%)		No Adjuvant Treatment 215 (69.8%)		
	#	%	#	%	p value
Clinical Stage					
IIA	18	19.4	57	26.5	0.200
IIB	13	14.0	26	12.1	
III	51	54.8	94	43.7	
IV	11	11.8	38	17.7	
Pathologic Stage					
No Evidence of Disease	20	21.5	61	28.4	0.263
I	12	12.9	32	14.9	
IIA	26	28.0	67	31.1	
IIB	15	16.1	17	7.9	
III	16	17.2	32	14.9	
IV	4	4.3	6	2.8	
Tumor Response to multimodality therapy					
Complete response	20	21.5	61	28.4	0.393
Partial response	50	53.8	100	46.5	
No response	23	24.7	54	25.1	

Table 2-3: Multivariable-Adjusted Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) Assessing the Association between Adjuvant Therapy and Mortality (N=308).

	Adjusted HR	95% CI	p value
Adjuvant Chemotherapy			
No	1.00	referent	
Yes	0.75	(0.55 - 1.01)	0.065
Age (years)	1.02	(1.00 - 1.03)	0.020
ASA score	1.21	(0.86 - 1.69)	0.276
Clinical Response			
Complete response	1.00	referent	
Partial response	1.65	(1.14 - 2.38)	0.008
No response	2.95	(1.97 - 4.41)	<0.001

ASA, American Society of Anesthesiologists

Table 2-4: Median Number of Chemotherapy Cycles, Performance Status, and Number of Grade 3 and Grade 4 Events for Patients receiving Adjuvant Chemotherapy Following Multimodality Therapy.

	Adjuvant Treatment (n=93)	
	No. of Subjects	
Median Chemo Cycles (IQR)	3 (1-5)	
ECOG Performance Status	0.5	
Adverse Events	Grade 3	Grade 4
Neutropenia	1	3
Thrombocytopenia	2	0
Thromboembolic Disease	2	0
Deep Vein Thrombosis	3	0
Bacteremia/Sepsis	1	1
Heart Failure	1	0
Pulmonary Embolism	0	1
Renal Dysfunction/Failure	2	0
Hyponatremia	1	0
Osteoporosis	1	0

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group

Table 2-5: Comparison of Median Survival between Patients Receiving Same or Different Adjuvant Chemotherapy Regimens Stratified by Clinical Response and Pathological Nodal Status for Partial Responders Only.

	Same Neoadjuvant and Adjuvant Treatment Regimens		***Different*** Neoadjuvant and Adjuvant Treatment Regimens		
	Median Months Survival (IQR)	No. of Subjects (N=49)	Median Months Survival (IQR)	No. of Subjects (N=44)	Log rank *p* value
Clinical Response					
Complete response	53.7 (29.7 – NYR)	10	37.6 (9.3 – NYR)	10	0.716
Partial response	52.7 (17.2 – NYR)	29	53.2 (18.8 – 93.6)	21	0.220
No response	29.3 (19.5 – 36.6)	10	23.8 (17.3 – 36.8)	13	0.914
Pathologic Nodal Status Amongst Partial Responders Only					
ypN0	NYR (16.6 – NYR)	24	30.3 (18.1 – 93.6)	11	0.152
ypN1	18.0 (11.1 – 41.9)	4	53.2 (18.8 – 63.5)	10	0.266

IQR, interquatile range; NYR, "Median Not Yet Reached"; ypN0 & ypN1, postoperative pathologic nodal status absence and presence, respectively.

Figure 2-1: Kaplan-Meier Estimates of Long-Term Survival Following Surgery for All Patients Receiving Adjuvant Chemotherapy vs. No Adjuvant Therapy

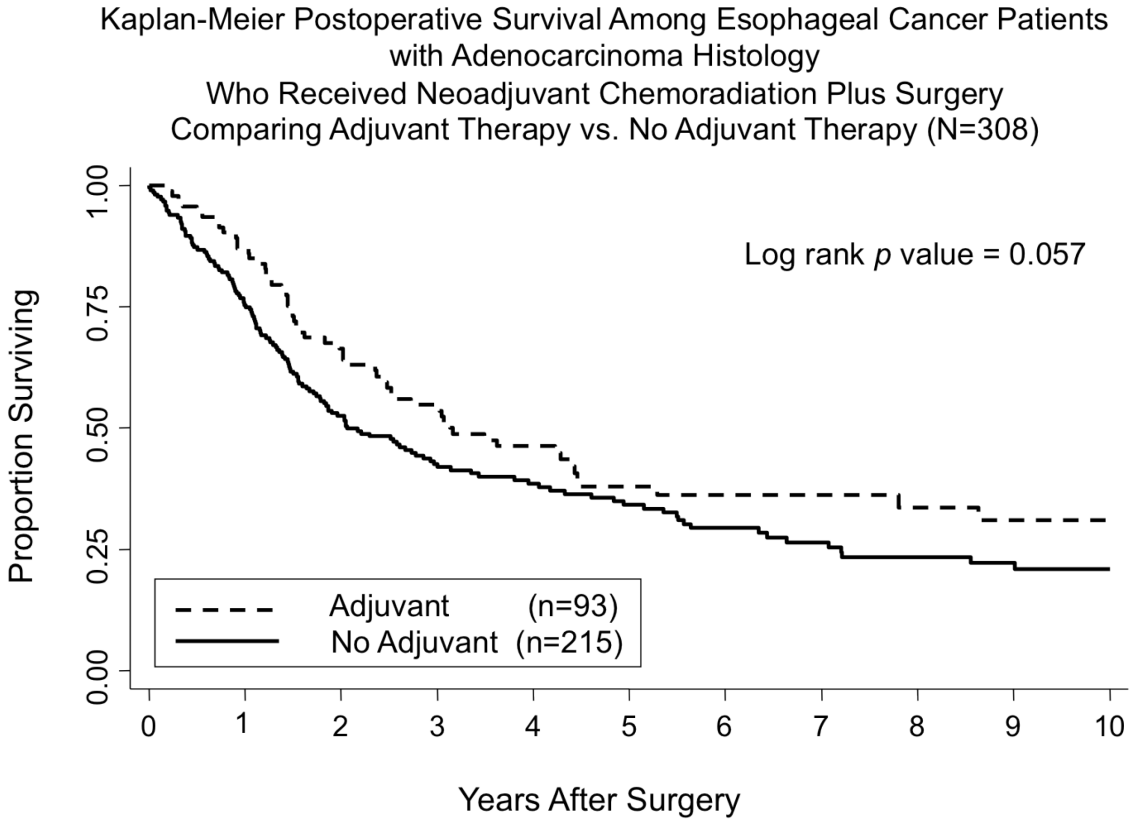


Figure 2-2: Kaplan-Meier Estimates of Long-Term Survival Following Surgery for All Patients Receiving Adjuvant Chemotherapy vs. No Adjuvant Therapy, Stratified by Clinical Response

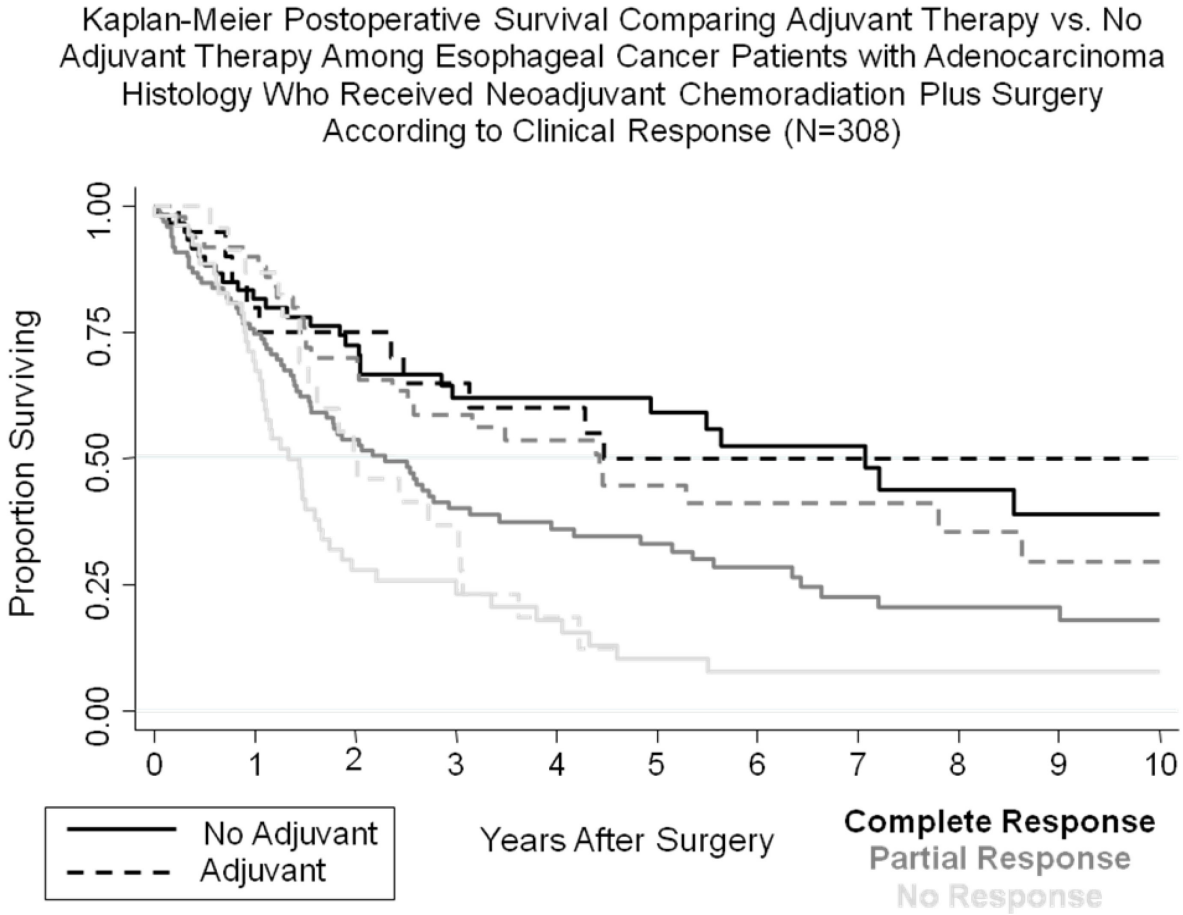
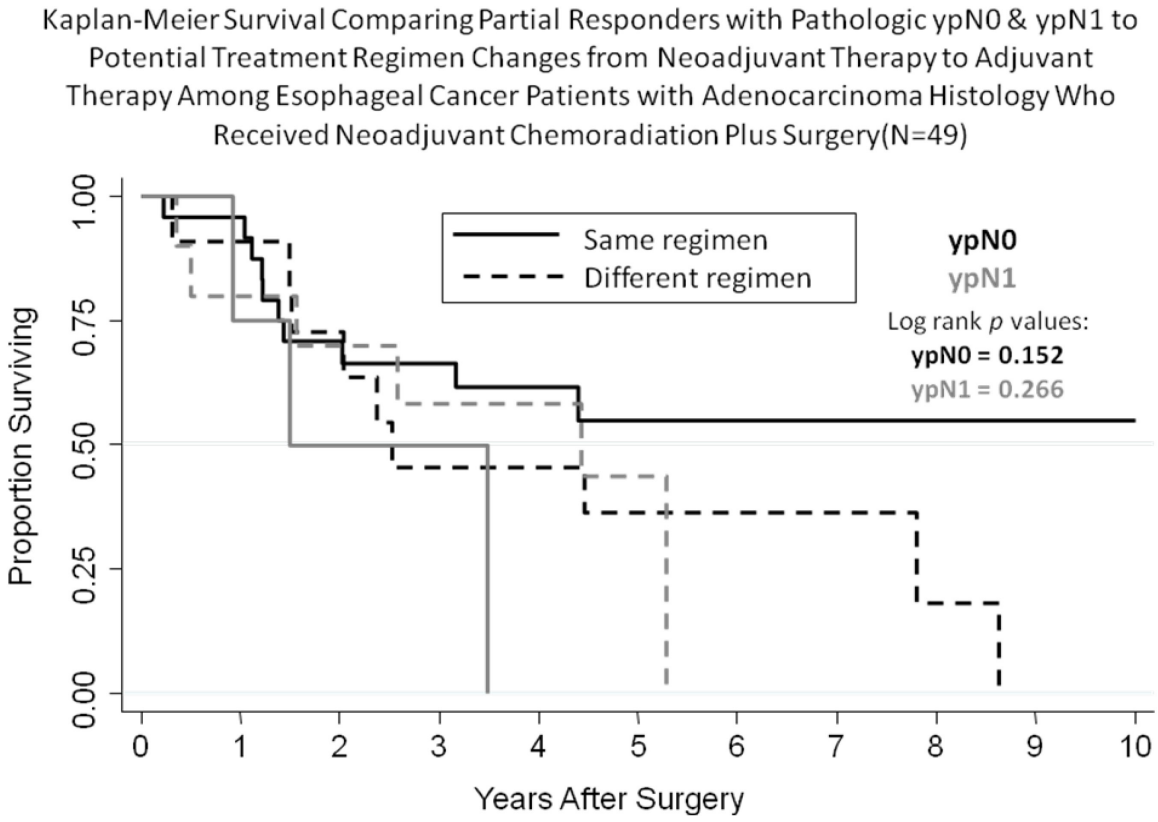


Figure 2-3: Kaplan-Meier Estimates of Long-Term Survival Amongst Partial Responders Receiving the Same vs. Different Adjuvant Chemotherapy Regimens, Stratified by Pathologic Nodal Status



CHAPTER 3

Examining Race Disparities in Surgical Recommendation and Survival Among Early Stage Non-Small Cell Lung Cancer Patients

Examining Race Disparities in Surgical Recommendation and Survival Among Early Stage Non-Small Cell Lung Cancer Patients

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Abstract

Background: The current understanding on racial disparities in receipt of potentially curative surgical therapy involves a complex interplay of multifactorial mechanisms. Identifying differences in factors related to patient, provider, and disease characteristics along the diagnosis-treatment continuum may offer insight on how to mitigate disparities in clinical decisions for optimal therapy.

Methods: A retrospective cohort study of patients in the Johns Hopkins Hospital Cancer Registry database who were diagnosed with stage I or II non-small cell lung cancer between 2000 and 2010 was conducted. Poisson regression with robust variance was used to estimate the prevalence ratio of surgical recommendation, which was reported as the relative risk (RR). Cox proportional hazards regression models estimated the adjusted hazard ratios (aHR) for all cause mortality.

Results: Among 904 white (81%) and black (19%) early-staged NSCLC patients, black patients were 8% less likely to be recommended surgical resection as compared to white patients (crude RR=0.92, 95% confidence interval [CI] 0.86 – 0.98). This association reduced to null after controlling for patient-, tumor-, physician-related factors (aRR=0.99, 95% CI 0.93 – 1.05). There was no significant association between race and mortality (aHR=1.17, 95% CI 0.89 – 1.55).

Conclusions: Race was not associated with surgical recommendation after adjusting for patient-, tumor-, and physician-related characteristics. Furthermore, race was not independently associated with mortality. Our study suggests recommendation for surgery differs by physician specialty and patient-physician encounter, yet these differences do not effect overall survival.

Introduction

Black patients with early-stage non-small cell lung cancer (NSCLC) have lower survival rates as compared to white patients, and this difference in outcome has been largely explained by the lower rates of surgical treatment among black patients [1, 2]. Lung cancer is the second most common malignancy and is the leading cause of cancer-related mortality in the U.S. [3]. Pulmonary surgical resection remains the primary and preferred approach to the treatment of stage I and II NSCLC [4, 5].

Several potential factors have been studied to better understand racial differences in the receipt of surgical treatment. Patient health-related factors that may be associated with racial differences in recommendation for surgical treatment include pulmonary lung function [6], co-morbidities [7], performance status, cigarette smoking [8], inadequate social support [2, 9], and access to care [10-13]. Also, patient belief patterns have been shown to effect the decision to undergo surgical treatment such as, beliefs about tumor spread on air exposure at the time of operation [14], and the possibility of cure without surgery, or simply refusal of surgery [15, 16]. Tumor-related factors such as advanced cancer stage at diagnosis and tumor histologic type help inform providers on therapeutic options such as surgery or systemic therapy [17, 18]. Finally, health care system and provider-related factors such as poor patient-provider communication such as discordant patient-provider race [19-22], distrust of the physician or healthcare system [22-24], and health care system and provider biases [24, 25] are often argued to be significant factors underlying racial disparities.

To better understand the factors influencing the recommendation for surgery including patient race, we conducted a retrospective cohort study. We hypothesized that

there would be no racial disparities among patients with early-stage NSCLC who received a surgical recommendation. We further hypothesized that overall survival would not differ by race once surgical recommendation was taken into account.

Methods

Study Population

A study population of 904 patients treated for early stage (IA-IIB), non-small cell lung cancer (NSCLC) at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins between January 1, 2000 and December 31, 2010 comprised the study cohort. Information on vital status and treatment was collected through May 31, 2012. Johns Hopkins Hospital (JHH) Cancer Registry personnel abstracted the medical record of patients treated in accordance with American College of Surgeon Guidelines.

The JHH Cancer Registry collects data on all patients diagnosed with and/or treated for lung cancer at JHH. Following national standards for data collection, coding, and staging, certified JHH tumor registrars collect data on incidences, primary site, histology, extent of disease, treatment, and outcomes. The JHH Cancer Registry assures lifetime follow-up of cancer patients and assures that 96% have current information within the last 14 months. The Johns Hopkins University School of Medicine Institutional Review Board approved this study. Information about patient-, tumor-, physician-related factors recommendation for surgical treatment and overall survival was considered for our study.

Exposure Assessment

Patient-Related Factors

Personal factors were provided in the JHH Cancer Registry record. Patient-related factors included race (white/black), age (continuous, <65, 65-74, and ≥75 years), gender (male or female), marital status (married or not married), smoking history (current, former, never, or unknown), health insurance at the time of diagnosis (yes/no), and Census tract median household income, which was obtained from the U.S. Census Bureau 2000 estimates. Patients were identified as having co-morbidities if they had one or more of the following co-morbidities defined by International Classification of Diseases, 9th Revision; [401.0 - 405.9 (hypertensive disease); 410.0 – 414.9 (Ischemic Heart Disease); 415.0 – 417.99 (diseases of pulmonary circulation); 420.0 – 429.9 (other forms of heart disease); 430.0 – 438.9 (cerebrovascular disease); 440.0 – 448.9 (diseases of arteries, arterioles, and capillaries); 451.0 – 459.9 (diseases of veins and circulatory system); 480.0 – 488.9 (pneumonia and influenza); 490.0 – 496.9 (chronic obstructive pulmonary disease)].

Tumor-Related Factors

Histological site (SEER) and stage were classified according to established American College of Surgeon conventions. Tumor characteristics included, year of diagnosis (2003 – 2009), histology (adenocarcinoma, squamous cell, bronchioalveolar carcinoma (BAC), adenosquamous, and non-small cell histology, not otherwise specified (NSCLC, not otherwise specified), stage (IA, IB, IIA, or IIB), surgical procedure (lobectomy, pneumonectomy, wedge resection, and segmentectomy). All surgical procedures were performed for curative intent.

Physician-Related Factors

Physician-specific factors collected were surgery recommending doctor's race, sex and sub-specialty (surgeon, oncologist, and pulmonologist).

Outcome

Surgical recommendation by initial surgery recommending physician was identified in the JHH Cancer Registry and confirmed by an audit of the patient's electronic records. Surgical recommendation was defined as recommended for surgery or not recommended for surgery by the initial surgery recommending physician. If the initial surgery recommending physician's sub-specialty was not surgery and did not recommend surgery, further patient chart review determined whether a surgeon was consequently consulted. While not included as an element of the definition for the outcome of surgical recommendation, patient refusal for surgical treatment was collected from the JHH Cancer Registry to provide further information on whether surgeons were consulted regarding the non-surgeon's decision not to recommend surgery. Reasons for not recommending surgery were collected and classified as "not part of the planned 1st course treatment", "contraindicated", "non-surgical procedure performed", or "unresectable".

Statistical Analysis

Comparison of means and medians of continuous variables was performed using the student *t* test (two-sided) and nonparametric Mann-Whitney U test, respectively. Comparisons between proportions for binary and categorical variables were performed using the chi-squared test for homogeneity. Fisher's Exact test was used to compare

differences in proportions when expected numbers in any cell were less than 5 units. All hypothesis tests were two-sided and results were considered statistically significant for p values ≤ 0.05.

We assessed univariate and multivariable associations between physician recommendation for surgery, defined as either surgery recommended or surgery not recommended with Poisson regression with robust variance to estimate the prevalence ratio. Poisson regression with robust variance was selected as the best statistical model because the proportion with surgical recommendation was greater than 10% [26]. We tested for interactions of selected covariates with race; of specific interest were median household income, co-morbidity, and physician sub-specialty. Poisson regression results were reported as relative risks (RR) with 95% confidence intervals (CIs).

Survival and the association of covariates were assessed using the Kaplan-Meier method and time to death was analyzed using the Cox proportional hazards model adjusted for multiple covariates. Survival was calculated from time of diagnosis to death or last follow-up. Differences in survival between groups were assessed using the log rank test. Cox regression results were reported as hazard ratios (HR) with 95% confidence intervals (CIs). Test based Schoenfeld residuals were used to confirm the proportional hazards assumption for the multivariable Cox regression model. All regression model analyses were performed using the STATA 10.0 statistical software (College Station, TX)

Results

A total of 904 NSCLC patients with stages IA to IIB were identified between years 2000 to 2010 and 19% were black race. Both race groups had similar gender distributions. Compared to whites, there was greater proportion of black patients who at time of diagnosis were age 65 or younger, not married, in the lowest quartile for median household income by Census tract, were current smokers, having histology other than adenocarcinoma, and had an initial consult with a non-surgeon. There were no statistically significant differences by race on distribution of tumor stage, surgical procedure, insurance coverage, or physician race (Table 3-1).

Black patients were recommended surgical resection less frequently than whites (84.3% vs. 91.7%, respectively, with an absolute difference of 7.4% less; $p<0.003$). In univariate analysis, black patients were 8% less likely to be recommended surgical resection as compared to white patients, which was statistically significant (RR=0.92, 95% confidence interval [CI] 0.86 – 0.98; Table 3-2). After controlling only for patient-related factors, the likelihood of recommendation for blacks remained stable but not statistically significant (aRR=0.95, 95% CI 0.88 – 1.02). While controlling only for tumor-related factors the likelihood for recommendation for surgery for blacks was reflective of the univariate model (aRR=0.92, 95% CI 0.86 – 0.99). After accounting for only physician-related factors, the association with race and recommendation was comparable with patient-related model (aRR=0.97, 95% CI 0.92 – 1.03). After fitting patient- , tumor-, and physician-related factors into the fully adjusted model there was no association of race and recommendation for surgery (aRR=0.99, 95% CI 0.93 – 1.05). In the physician-related and fully adjusted model, non-surgeons were significantly

negatively associated with surgical recommendation as compared to surgeons (aRR=0.47, 95% CI 0.38 – 0.58).

Figure 3-1 shows overall survival after diagnosis by race and recommendation for surgery. Among patients recommended for surgery, black patients have poorer overall survival compared to white patients. The unadjusted medians and 5-year survival rates after diagnosis for whites compared to blacks was 6.07 years; 5-year 56% versus 4.28; 5-year 44%, respectively (log rank test p=0.032). Interestingly, the opposite was observed among patients not recommended for surgery (test for interaction, p=0.108). However, the difference in survival was not statistically significant. Among cases not recommended surgery, black patients had improved survival after diagnosis (median years 2.12; 5-year 22%) as compared to white patients (median years 1.03; 5-years 20%; log rank p=0.185).

The unadjusted HR for all cause mortality among black patients was elevated by 26% as compared to white patients with marginal statistical significance (HR=1.26, 95% CI 0.99 – 1.60; Table 3-3). After adjusting for physician recommendation, patient- and tumor-related characteristics, the race association was attenuated (aHR=1.17, 95% CI 0.89 – 1.55), while recommendation for surgery remained stable in the mortality hazard model (aRR=0.38, 95% CI 0.28 – 0.51).

Table 3-4 describes the distribution of characteristics among those patients who were not recommended surgery according to race, and consequently showed no differences by race. Of the 88 patients not recommended for surgery, 31% were black. Comparing proportions in whites versus blacks, reasons why patients were not recommended surgery included, 1) *not part of planned 1st course treatment* (46% vs. 22%), 2) *contraindication* (31% vs. 48%), 3) *non-surgical procedure was performed*

(13% vs. 22%), and 4) *tumor was deemed to be unresectable* (10% vs. 7%). Blacks patients tended to have more co-morbidities than whites (70% vs. 57%; p=0.248), respectively. The majority of both patient groups were seen by a non-white physician, 61% for whites and 74% in blacks (p=0.224). There were no differences in distribution by race for referring physician sub-specialty.

Among non-surgeons who were the initial referring physician (n=104), Table 3-5 shows the proportion by race if a surgeon was consulted regarding the recommendation for or against surgery. There was no difference by race in the proportion of surgeons consulted when a non-surgeon did not recommend surgery (p=0.777) and no patient went on to get surgery if not recommended whether or not the surgeon was consulted. Although there was a difference in proportion of surgery consults by race among non-surgeons that recommended surgery, those patients that did not subsequently consult a surgeon actually refused treatment. Patient refusal for surgery did not differ by race (p=0.242).

Discussion

This study reported the association between patient's race and likelihood of surgical recommendation after accounting for patient-, tumor-, and physician-related factors, and overall survival after adjustment for both recommendation and race among early stage NSCLC patients. In this study black patients were recommended for surgery 8% less than white patients, but after accounting for patient-, tumor-, and physician-related factors the association was reduced to approaching null. After accounting for recommendation for surgery, patient- and tumor-related factors, the HR for all cause mortality for black race

was attenuated to aHR=1.17 and lost statistical significance. There were no characteristics disproportionate by race when not recommended surgery and surgeons tended to concur with treatment recommendations of non-surgeons. Race as a risk factor alone was not independently associated with surgical recommendation or overall survival. Our analysis suggests that patient-, tumor- and physician-related factors have a greater influence in the treatment recommendation process than racial characteristics alone.

Findings from this investigation suggest that consultation for surgical treatment at our institution was equally accessible regardless of patient race. Table 3-4 showed no differences by race among patients not recommended for surgery on factors influential on physician recommendation. Additionally, as shown in Table 3-5, patients whose initial physician encounter was with a non-surgeon, the recommendation not to have surgery was subsequently followed-up by a surgeon consult and was comparable by race. Furthermore, patients who were recommended for surgery but did not subsequently consult a surgeon ultimately decided to forego surgery. The reason for a patient not undergoing surgery was not within the scope of this investigation however those reasons are of great clinical interest and concern.

Some studies that examined racial disparities in receipt of lung cancer surgery among those recommended for surgery have found patient refusal rates higher among black patients than white patients [16, 24]. They proposed factors such as distrust of the healthcare team, cultural beliefs, and limited access to subspecialty care as substantial reason for refusal. Although receipt of surgery was not the aim of our investigation, we

also observed a marginal elevated refusal rate for surgery in blacks (11/19) 58% compared to whites (8/19) 42%.

Reasons for patient refusal for surgery may be personal decisions guided by numerous and complex issues, directly or indirectly associated with their socioeconomic environment. Sub-analysis found that 19 patients refused surgical treatment after the physician recommendation for surgery. Among these patients, 68% (13/19) were in the lowest tertile of median household income by Census tract ($8,365 - $36,045), and all of these patients resided in Baltimore City while the other 6 patients lived in distant counties with median household income by Census tract ranging between $43,031 and $107,735. Patient refusal for surgery in our study might be explained by financial stressors and loss of work or income during the surgical procedure and recovery process. In addition, 79% (15/19) were not married, which may have also influenced patient refusal for surgery given the lack of supportive home care and even the lack of supplementary financial support, usually provided by a spouse.

It has been proposed that black patients may tend to present with more severe comorbidities than white patients thereby precluding them from surgical recommendation [27]. We found no differences in proportion of having one or more comorbidities by race. However, prevalence of comorbidities was a significant independent covariate with an 8% reduced probability for recommendation and the association remained stable even after adjustment for other patient-, tumor-, and physician-related factors (Table 3-2). However, after adjustment, prevalence of comorbidities was not a significant risk factor for overall survival in our study which we suggest that the severity of the comorbidities do not differ between white and black patients. The relative severity of having a co-

morbidity may not have outweighed the risk compared to the outcome of not undergoing lung cancer surgery [7]. Current smoking was associated with increased HR for mortality (aHR=1.53 95% CI 1.00 – 2.35). It is possible that more severe co-morbidities, such as chronic obstructive pulmonary disease and poor pulmonary function are also associated with heavy smoking-related behaviors thereby precluding some patients from surgical recommendation.

Another finding from our investigation showed married individuals have a greater probability for surgical recommendation and have better survival compared to non-married individuals, independent of other patient, tumor and physician-related factors. Our finding is not novel. Pruuthi et al, studied patients undergoing cystectomy for bladder cancer and found married individuals had improved perioperative, and postoperative survival outcomes compared to unmarried patients[28]. The benefits of marriage underscore the dynamic of healthy behaviors and actions that can effect timely and positive clinical decisions when reinforced by positive social support.

A sub-analysis revealed reasons why patients were not recommended for surgery. While the distributions did not differ statistically significantly by race, reasons include ‘surgery was not part of the planned first course’ for the majority of whites while the majority of black patients had recorded ‘contraindication’ as the reason why not recommended. These reasons might indicate more patients with stage closer to IIB where neoadjuvant radiation is often recommended. Twenty-eight percent of patients not recommended for surgery were stage IIBcompared to 14% of patients recommended for surgery. Perhaps these patients have more severe comorbidities possibly related to heavy, long-term cigarette smoking. An alternative consideration as a reason why surgery was

not recommended among this group might be due to the increasing use of new and effective non-surgical procedures, such as dose-intensified conformal radiation therapy and radiofrequency ablation [29].

The majority of black patients in our study resided in Baltimore City (64%), while a minority of white patients resided in Baltimore City (11%). It may be that patients from other residential areas who were referred to Hopkins have better access to care and came to Hopkins with the intention of surgery. Whereas Baltimore City residents might not have had a similar system of care that facilitate medical examinations to identify cancer in a timely manner. However, we did collect information on insurance, median household income by Census tract, co-morbidities, and stage of disease. Only stage and the presence of one or more co-morbidities were statistically associated with surgical recommendation. We were not able to definitively assess whether a patient was first diagnosed at our institution or referred to our institution after initial diagnostic assessment. There might be patient or cultural characteristics about those who reside in Baltimore City that differ from those who were referred to our institution for care which may limit generalizability.

Recommendation of surgery may vary how it is measured because recommendation is "defined" by sub-specialties differently. This was a concern to the investigators since different sub-specialties have different clinical perspectives. We were able to collect information on the specialty of physician as surgeon, oncologist, or pulmonologist. Physician specialty was accounted for in the regression for surgical recommendation. Compared to surgeons, pulmonologists and oncologists were significantly less likely to provide a recommendation for surgery, a finding that remained

statistically significant after adjustment of patient-, tumor- and physician-related factors. Given the distribution of physician specialty varied by patient race, institutions should more closely evaluate how black and white patients enter into initial specialty encounters.

Physician recommendation is not independent of the patient preferences and input. Physicians do take patient opinion into account before making a recommendation. It could be that a patient might not have felt comfortable with surgery as an option and opted for non-surgical procedure and hence the observed a recommendation of "no surgery". Another limitation might be how the recommendation for surgery was measured that caused potential residual confounding.

A statistical strength of this study was the use of statistical models that directly measured the prevalence ratio of surgical recommendation by race. Unlike several prior studies that utilized logistic regression to model the relationship between race and receipt of surgical treatment, our study modeled the association between race and surgical recommendation as prevalence ratios using Poisson regression with robust variance given that the prevalence of recommendation in our study population was 90%. The odds ratio from logistic regression would have over-estimated the relative risk and log-binomial regression often has convergence issues [26]. In addition, we were able to examine physician recommendation for surgery separate from receipt of surgery, which makes this investigation unique from many other studies focused on racial disparities and surgical treatment alone.

Conclusions

To summarize, after accounting for patient-, tumor-, and physician-related factors race was not independently associated with physician recommendation for surgery or survival. Recommendation and receipt of definitive surgery is strongly associated with greater survival. Given the nature of the clinical setting, findings from this study may not be widely generalizable beyond high volume medical institution settings similar to that of Johns Hopkins Hospital. However, our results may aid clinicians in identifying patients that are medically eligible for curative surgery but are at most risk to refuse surgical treatment due to socioeconomic disadvantages. More prospective clinical cohort studies are needed to examine the underlying reasons for patient refusal for definitive surgery.

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Table 3-1. Characteristics of the Study Population by Race, Johns Hopkins Hospital. (N=904)

	White 732 (81.0%)		**Black** 172 (19.0%)		
Characteristics	#	**%**	#	**%**	p value*
Sex					0.859
Male	352	48.1	84	48.8	
Female	380	51.9	88	51.2	
Median Age, years & IQR	68	61-75	64	57-71	<0.001
Age, years					0.003
<65	278	38.0	88	51.2	
65 – 74	263	35.9	55	32.0	
≥75	191	26.1	29	16.8	
Married					<0.001
Not Married	246	33.6	105	61.1	
Married	486	66.4	67	38.9	
Insurance Coverage					0.098
No	10	1.4	6	3.5	
Yes	722	98.6	166	96.5	
Median Household Income, 2000 US Census Tract (Quartiles)					<0.001
Q1 $7,944 - $34,922	117	16.3	105	62.5	
Q2 $34,943 - $47,759	194	27.0	30	17.9	
Q3 $47,778 - $65,156	199	27.7	21	12.5	
Q4 $65,278 - $177,098	209	29.1	12	7.1	
Co-Morbidities					0.759
None	418	57.1	96	55.8	
1 or more	314	42.9	76	44.2	
Smoking Status					0.001
Never	71	9.7	11	6.4	
Former	435	59.4	82	47.7	
Current	226	30.9	79	46.0	
Histology					0.008
Adenocarcinoma	357	48.8	79	45.9	
Squamous cell	194	26.5	56	32.6	
Large cell	16	2.2	6	3.5	
BAC	104	14.2	9	5.2	
NSCLC, nos	51	7.0	17	9.9	
Adenosquamous	10	1.3	5	2.9	
Stage					0.114
IA	331	45.2	79	45.9	
IB	249	34.0	54	31.4	

IIA	47	6.5	5	2.9	
IIB	105	14.3	34	19.8	
Surgical Procedure					0.732
Lobectomy	545	82.2	112	83.6	
Pneumonectomy	22	3.3	2	1.5	
Wedge Resection	66	10.0	14	10.4	
Segmentectomy	30	4.5	6	4.5	
Surgery Recommending Physician Specialty					
Surgeon	663	90.6	137	79.6	<0.001
Oncologist	41	5.6	17	9.9	
Pulmonologist	28	3.8	18	10.5	
Surgery Recommending Physician Race					0.063
White	211	28.8	62	36.1	
Non-White	521	71.2	110	63.9	

* Nonparametric Mann-Whitney U test and X^2 test for homogeneity
IQR, interquartile range; NSCLC, nos, non-small cell lung cancer, not otherwise specified; BAC, bronchioloalveolar carcinoma

Table 3-2. Crude and Adjusted Relative Risks and 95% Confidence Intervals (CI) with Robust Variance Assessing the Association Between Race and Surgical Recommendation Among Early Stage Non-Small Cell Lung Cancer Patients. (N=904)

	Univariate			Patient-Related Factors			Tumor-Related Factors			Physician-Related Factors			Full Adjusted		
	Crude Relative Risk[1]	95% CI	p value	Adjusted Relative Risk[2]	95% CI	p value	Adjusted Relative Risk[3]	95% CI	p value	Adjusted Relative Risk[4]	95% CI	p value	Adjusted Relative Risk[5]	95% CI	p value
Race															
Caucasian	1.00	referent		1.00	referent		1.00	referent		1.00	referent		1.00	referent	
African-American	0.92	(0.86 - 0.98)	0.016	0.95	(0.88 - 1.02)	0.152	0.92	(0.86 - 0.99)	0.009	0.97	(0.92 - 1.03)	0.369	0.99	(0.93 - 1.05)	0.737
Age (years)	1.00	(1.01 - 1.03)	0.148	1.00	(0.99 - 1.00)	0.163	1.00	(0.99 - 1.00)	0.100	1.00	(1.00 - 1.01)	0.041	1.00	(0.99 - 1.01)	0.192
Marital Status															
Not Married	1.00	referent		1.00	referent								1.00	referent	
Married	1.07	(1.02 - 1.13)	0.003	1.06	(1.01 - 1.11)	0.028							1.04	(0.99 - 1.08)	0.074
Median Income, Dollars (Quartile)															
Q1 ($7,944 - $34,922)	1.00	referent		1.00	referent								1.00	referent	
Q2 ($34,943 - $47,759)	1.05	(0.98 - 1.13)	0.191	1.02	(0.95 - 1.10)	0.522							1.01	(0.95 - 1.07)	0.866
Q3 ($47,778 - $65,156)	1.11	(1.04 - 1.18)	0.002	1.08	(1.01 - 1.15)	0.030							1.02	(0.97 - 1.08)	0.435
Q4 ($65,278 - $177,098)	1.08	(1.01 - 1.15)	0.028	1.04	(0.97 - 1.12)	0.255							1.00	(0.94 - 1.05)	0.933
Co-morbidities															
None	1.00	referent		1.00	referent								1.00	referent	
≥1	0.92	(0.88 - 0.97)	0.001	0.93	(0.89 - 0.97)	0.002							0.93	(0.90 - 0.97)	0.001
Histology															
Adenocarincoma	1.00	referent					1.00	referent					1.00	referent	
Squamous cell	0.92	(0.88 - 0.97)	0.003				0.94	(0.90 - 0.99)	0.027				0.96	(0.92 - 1.00)	0.064
Other histology*	0.90	(0.85 - 0.96)	0.001				0.90	(0.85 - 0.96)	0.001				0.93	(0.88 - 0.98)	0.006
Stage															
IA	1.00	referent					1.00	referent					1.00	referent	
IB	0.94	(0.90 - 0.99)	0.014				0.95	(0.90 - 0.99)	0.024				0.96	(0.92 - 0.99)	0.048
IIA	0.96	(0.88 - 1.05)	0.385				0.95	(0.87 - 1.04)	0.245				0.96	(0.89 - 1.04)	0.342
IIB	0.87	(0.80 - 0.95)	0.001				0.87	(0.81 - 0.95)	0.001				0.91	(0.86 - 0.98)	0.009
Physician Specialty															
Surgeon	1.00	referent								1.00	referent		1.00	referent	
Non-surgeon**	0.46	(0.37 - 0.57)	<0.001							0.46	(0.37 - 0.57)	<0.001	0.47	(0.38 - 0.58)	<0.001
- (log likelihood)				*880.747*			*897.315*			*882.762*			*864.428*		

* Other histology- large cell, bronchioloalveolar carcinoma, NSCLC, nos, and adenosquamous

** Non-surgeon- pulmonologist or oncologist

Crude Model 1- (Univariate).

Adjusted Model 2- (Patient-related) adjusted for race, age, marital status, median household income, and comorbidities.

Adjusted Model 3- (Tumor-related) adjusted for race, age, histology and stage.

Adjusted Model 4- (Physician-related) adjusted for race, age, physician specialty.

Adjusted Model 5- (Full Adjusted) adjusted for race, age, marital status, median household income, comorbidities, histology, stage, physician specialty.

Physician Race was not statistically significant by univariate analysis and not included in table 3-2.

Relative risks represent prevalence ratios

Table 3-3. Crude and Adjusted Hazard Ratios and 95% Confidence Intervals (CI) Assessing the Association Between Race and Mortality Among Early Stage Non-Small Cell Lung Cancer Patients. (N=904)

	Crude Hazard Ratio	95% CI	p value	Adjusted Hazard Ratio†	95% CI	p value
Race						
Caucasian	1.00	referent		1.00	referent	
African-American	1.26	(0.99 - 1.60)	0.058	1.17	(0.89 - 1.55)	0.259
Age (years)	1.02	(1.01 - 1.03)	<0.001	1.02	(1.01 - 1.03)	<0.001
Sex						
Male	1.00	referent		1.00	referent	
Female	0.80	(0.66 - 0.97)	0.022	0.71	(0.57 - 0.88)	0.002
Marital Status						
Not Married	1.00	referent		1.00	referent	
Married	0.75	(0.61 - 0.91)	0.003	0.78	(0.63 - 0.97)	0.026
Median Income, Dollars (Quartile)						
Q1 ($7,944 - $34,922)	1.00	referent		1.00	referent	
Q2 ($34,943 - $47,759)	1.07	(0.82 - 1.39)	0.632	1.20	(0.90 - 1.60)	0.222
Q3 ($47,778 - $65,156)	0.95	(0.72 - 1.25)	0.695	1.22	(0.90 - 1.65)	0.203
Q4 ($65,278 - $177,098)	0.92	(0.70 - 1.22)	0.569	1.18	(0.86 - 1.61)	0.313
Comorbidities						
None	1.00	referent		1.00	referent	
1 or more	1.20	(0.98 - 1.46)	0.072	1.02	(0.82 - 1.25)	0.886
Smoking Status						
Never	1.00	referent		1.00	referent	
Former	1.44	(0.97 - 2.15)	0.071	1.27	(0.84 - 1.91)	0.254
Current	1.62	(1.07 - 2.44)	0.022	1.55	(1.01 - 2.38)	0.045
Histology						
Adenocarincoma	1.00	referent		1.00	referent	
Squamous cell	1.38	(1.10 - 1.73)	0.006	0.97	(0.76 - 1.24)	0.822
Other histology*	1.20	(0.94 - 1.52)	0.140	1.15	(0.90 - 1.46)	0.275
Stage						
IA	1.00	referent		1.00	referent	
IB	1.53	(1.22 - 1.92)	<0.001	1.49	(1.18 - 1.88)	0.001
IIA	1.34	(0.83 - 2.16)	0.232	1.37	(0.84 - 2.22)	0.203
IIB	2.91	(2.24 - 3.78)	<0.001	2.93	(2.23 - 3.85)	<0.001
Recommended for Surgery						
Not Recommended	1.00	referent		1.00	referent	
Recommended	0.32	(0.25 - 0.43)	<0.001	0.38	(0.28 - 0.51)	<0.001

* Other histology- large cell, bronchioloalveolar adenocarcinoma (BAC), NSCLC, nos, and adenosquamous
† Adjusted for recommendation for surgery, race, age at diagnosis, sex, marital status, median household income, comorbidities, smoking status, histology, and stage.

Table 3-4. Distribution of Characteristics for Patients Not Recommended by Race. (N=88)

	White 61 (69.3%)		**Black** 27 (30.7%)		
	#	**%**	**#**	**%**	p value
Reasons Why Not Recommended					0.143**
Not part of the planned 1st course	28	45.9	6	22.2	
Contraindicated	19	31.2	13	48.2	
Non-surgical procedure performed	8	13.1	6	22.2	
Tumor unresectable	6	9.8	2	7.4	
Stage					0.415**
IA	17	27.9	7	25.9	
IB	24	39.3	10	37.0	
IIA	5	8.2	0	0.0	
IIB	15	24.6	10	37.0	
Married	30	49.2	10	37.0	0.291*
1 or more co-morbidities	35	57.4	19	70.4	0.248*
Smoking status					0.150**
Never	7	11.4	0	0.0	
Former	34	55.7	15	55.6	
Current	20	32.8	12	44.4	
Surgery Recommending Physician's Race					0.224*
White	24	39.3	7	25.9	
Non-White	37	60.7	20	74.1	
Surgery Recommending Physician's Specialty					0.483*
Surgeon	22	36.1	8	29.6	
Pulmonologist	19	31.2	12	44.4	
Oncologist	20	32.8	7	25.9	

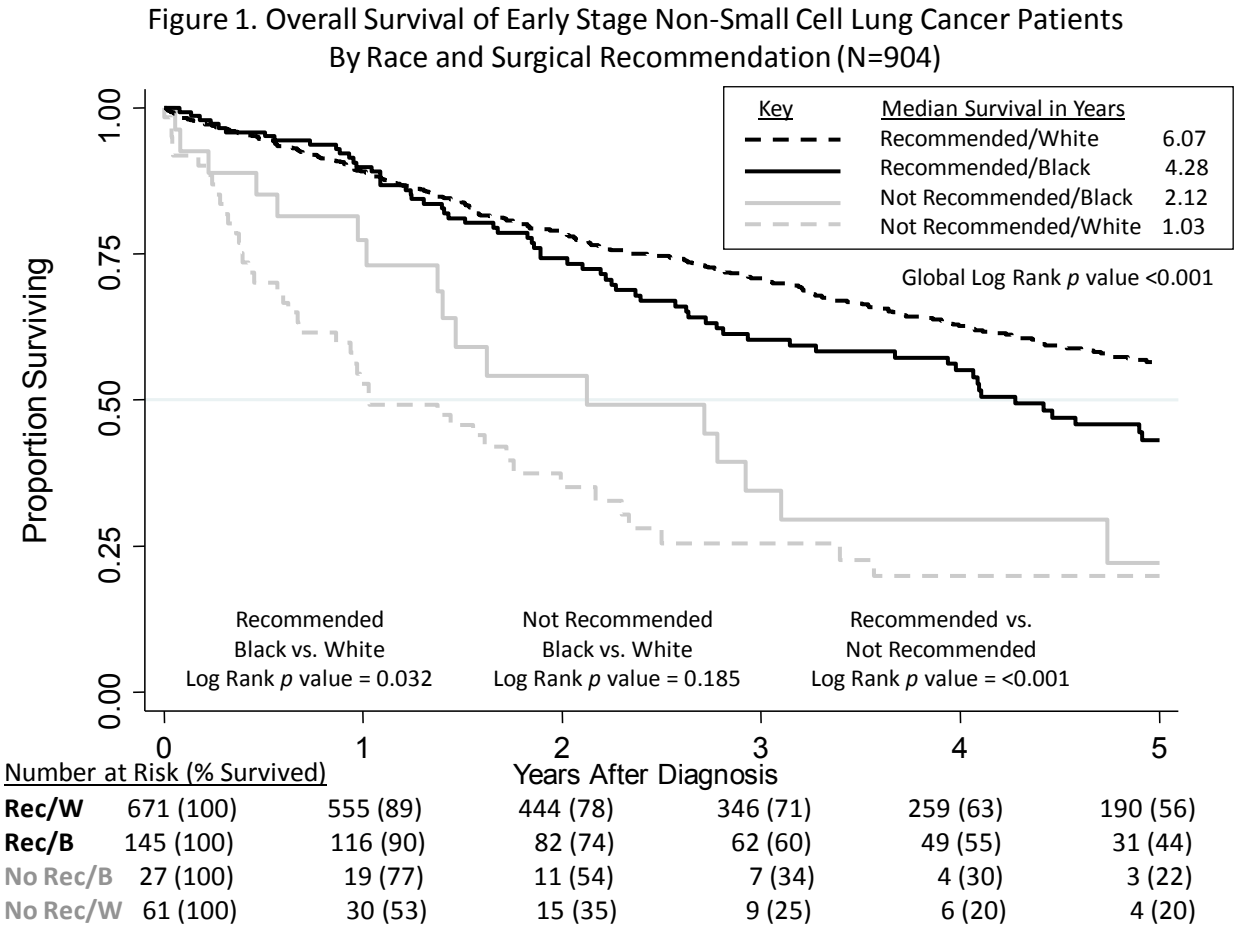
* Fishers Exact
** Chi-squared test for homogeneity

Table 3-5. Was a Surgeon Consulted on Non-Surgeon's Recommendation by Race? (Non-surgeon subset, n=104)

	Non-Surgeon Recommended Surgery* (n=46)					Non-Surgeon Recommended No Surgery** (n=58)				
	White 30 (65.2%)		Black 16 (34.8%)			White 39 (67.2%)		Black 19 (32.8%)		
	#	%	#	%	p value	#	%	#	%	p value
Surgeon consulted about non-surgeon recommendation					0.001					0.777
No	3	10.0	9	56.2		32	82.1	15	79.0	
Yes	27	90.0	7	43.8		7	17.9	4	21.0	
Patient refused treatment					0.242					
No surgeon consult	3	60.0	9	90.0						
Surgeon consult	2	40.0	1	10.0						

* Of those recommended surgery and surgeon did not concur, all patients refused further treatment thus surgery consult never occurred.
** Of those patients who were not recommended for surgery, no patient chose surgery.

Figure 3-1: Overall Survival of Early Stage Non-Small Cell Lung Cancer Patients by Race and Surgical Recommendation (N=904)



CHAPTER 4

Human Immunodeficiency Virus Infection as a Prognostic Factor in Surgical Patients with Non-Small Cell Lung Cancer

Human Immunodeficiency Virus Infection as a Prognostic Factor in Surgical Patients with Non-Small Cell Lung Cancer

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Abstract

Background: To assess the effect of HIV-infection on post-operative survival among non-small cell lung cancer (NSCLC) patients.

Methods: A retrospective cohort study compared 22 HIV-infected lung cancer patients to 2,430 lung cancer patients with HIV-unspecified status resected at Johns Hopkins Hospital between 1985-2009. Sub-cohort comparative analyses were performed using individual matching methods.

Results: Thirty day mortality rates did not differ between HIV-infected and HIV-unspecified patients. Long-term survival rates in HIV-infected lung cancer patients were significantly shorter than in HIV-unspecified patients (median 26 vs. 48 months; p=0.001). After adjustment, the HR of mortality among HIV-infected NSCLC patients was ≥3 fold that of HIV- unspecified patients (aHR=3.08, 95% CI 1.85-5.13). When additional surgical characteristics were modeled in a matched sub-cohort, the association remained statistically significant (aHR=2.31, 95% CI 1.11-4.81). Moreover, HIV-infected lung cancer patients with CD4 counts <200 cells/mm^3 had shortened median survival than those with CD4 ≥200 cells/mm^3 (8 vs. 40 months; p=0.031). Postoperative pulmonary and infectious complications were also elevated in the HIV-infected group (p=0.001 and <0.001, respectively). After surgery, median time to cancer progression was shorter among HIV-infected patients (20.4 months) versus HIV-unspecified patients (p=0.061).

Conclusions: Although surgery in HIV-infected NSCLC patients has comparable 30-day mortality to HIV-unspecified NSCLC patients, it is associated with more postoperative complications, more rapid progression to disease recurrence and poorer long-term

survival. Optimizing immune status prior to surgery and careful patient selection based on DLCO may improve patient outcomes.

Introduction

Numerous epidemiologic studies have noted an elevated risk of lung cancer among HIV-infected individuals [1-5]. Typically, these patients are younger, have advanced disease stage, and worse overall survival compared to the general population [6-8]. In fact, so advanced is their stage at presentation, that only 10-15% of HIV lung cancer patients can undergo curative resection [7]. No single institution has accumulated a large experience with these patients, and to date, little is known about the clinical efficacy of surgical resection in HIV-infected non-small cell lung cancer (NSCLC) patients. Due to the small number of patients with early disease, only a few authors have reported on surgical outcomes in this patient population [9-18] with a cumulative total in the literature fewer than 25 patients. The present general consensus based on this limited sample size has been to offer surgery with curative intent to HIV-infected NSCLC patients, regardless of their immune state, if there is localized disease and good patient performance status [9, 16].

Despite few HIV surgical patients with NSCLC in the literature, as a single institution, we have resected 22 HIV-infected NSCLC patients. We performed a retrospective cohort study to examine differences in characteristics and survival between HIV-infected and HIV-unspecified NSCLC patients who underwent surgery for curative intent at Johns Hopkins Hospital from 1985 to 2009.

Methods

Study Population

The HIV infection status of 10,122 lung cancer patients treated between January 1, 1975 and December 31, 2009, was determined by cross-referencing the Johns Hopkins HIV specialty clinic and the Johns Hopkins Hospital Cancer Registry. Consequently, 124 HIV-infected patients with lung cancer were identified. Since the first HIV-infected lung cancer patient at Johns Hopkins was diagnosed on August 15, 1985, 2,162 patients diagnosed prior to 1985 were excluded. Any cancer types other than NSCLC were excluded, which subsequently removed 914 patients; 10 of whom were HIV-infected patients. Of the remaining 7,033 NSCLC patients, 4,581 (65%) received no surgical intervention, of which 92 were HIV-infected. The final study population comprises 2,452 NSCLC patients who underwent surgery for curative intent, of which 22 were HIV-infected. Johns Hopkins Institutional Review Board approved this study.

Exposure of Interest

HIV infection was defined as being HIV-serostatus positive in the Johns Hopkins HIV specialty clinic database prior to pathologic confirmed diagnosis of NSCLC. Persons with NSCLC who were not identified as HIV-serostatus positive after cross-referencing the Johns Hopkins HIV specialty clinic and the SPORE Lung Cancer database were classified as HIV-unspecified.

Exposure Assessment

Demographic characteristics, NSCLC subtypes, cancer staging, oncologic treatment, American Anesthesiology Classification morbidity index, HIV/AIDS-related

information, and associated risk factors were obtained from the Johns Hopkins SPORE lung cancer database, clinical charts, and the institution's tumor registry using standardized collection forms and quality controlled data entry procedures. Surgical procedures for curative intent were defined as lobectomy, bilobectomy, or pneumonectomy. Sublobar resections were considered curative only when the surgeon documented this intent.

Outcome Ascertainment

The primary end point was postoperative survival. Study entry was defined as date of surgery. Patients were followed until date of death, lost to follow-up, or administratively censored five years after resection. Vital status was confirmed with clinical records, death certificates, and the Social Security Death Index. The secondary end point was disease progression after surgery.

Individual Matching

Since HIV-infected lung cancer patients are younger compared to the general population [19] and other clinical characteristics related to survival can be disproportionately distributed by HIV status, such as cancer stage, histology, race, sex, NSCLC diagnosis prior to and after HAART era, and even socioeconomic status [7, 8, 16, 19, 20], we attempted to achieve "balance" on the distribution of observed factors that might potentially bias the effect of HIV on survival [21]. Therefore, a representative sub-cohort was drawn from the surgical cohort; 3 HIV-unspecified surgical patients were individually matched to each HIV-infected surgical patient by age at NSCLC diagnosis,

sex, race, stage, NSCLC histologic subtype, date of surgery (+/- 5 years), and surgical procedure.

Statistical Analysis

Comparison of means and medians of continuous variables was performed using the Student's *t*-test (two-sided) and nonparametric Mann-Whitney U test, respectively. Comparisons between proportions for binary and categorical variables were performed using the χ^2 test for homogeneity or Fisher's exact test. All hypotheses tests were two-sided, and results were considered statistically significant for p values <0.05.

Survival was illustrated using the Kaplan-Meier method, and the association of covariates with time to death was analyzed using the Cox proportional hazards regression model. In the multivariable models, covariate adjustment for the larger (unmatched) surgical cohort was ultimately determined by differences in HIV status on observed characteristics within the entire cohort, prior belief, as well as clinical and biological plausibility. The individual matched sub-cohort analysis included all the covariates in the unmatched regression model, postoperative complications, and matched covariates. Results of Cox regression are reported as hazard ratios (HR) with 95% confidence intervals (CIs).

Covariates used for matching methods remained in the multivariable model to account for residual confounding. A test on the basis of Schoenfeld residuals confirmed the proportional hazards assumption for the matched sub-cohort multivariable Cox regression model (p=0.993). Stage presented in the regression models was treated as a continuous variable when tested for trend.

A post-hoc sensitivity analysis was conducted to account for potential bias related to secular changes in overall survival due to the introduction of HAART. We restricted our analytic cohort to only patients diagnosed with lung cancer during HAART (≥1996). Statistical analyses were performed using STATA 10.0 statistical software (College Station, TX).

Results

Our NSCLC cohort consisted of 7,033 patients of which 114 HIV-infected NSCLC patients were identified. Among the HIV-infected individuals, 19% (22/114) underwent surgery for curative intent versus 35% (2,430/6,919) of HIV-unspecified individuals. In contrast to the HIV-unspecified patients, HIV-infected patients were significantly younger, African-American, and male (Table 4-1). Both groups were typical of a surgical cohort, each with a similar stage of disease with stage I predominating. In both groups, a lobectomy was the preferred procedure, and most patients had adenocarcinoma. Likely due to younger age, HIV-infected patients smoked fewer pack-years compared to HIV-unspecified patients, 43 versus 54 pack-years, respectively (p=0.012). HIV-infected patients were more likely to have had a longer delay from diagnosis to surgery.

Entire Cohort (Unmatched)

The 30-day mortality among HIV-infected and HIV-unspecified patients in the large analytic set did not differ and was 0% and 2.3%, respectively (Table 4-1). The post-surgical median survival for HIV-infected patients was shorter at 26.4 months vs. 48.4 months for HIV-unspecified patients (p=0.001; Figure 4-1). HIV-infection alone

conveyed a HR of long-term mortality of more than twice that of HIV-unspecified patients (unadjusted hazard ratio = 2.24, 95% CI 1.37-3.68; Table 4-2). After adjusting for risk factors related to overall survival among surgical patients into the multivariable Cox regression model, the relative hazard of mortality in the HIV-infected group increased and remained statistically significant (adjusted HR (aHR) =3.08, 95% CI 1.85-5.13; Table 4-2).

Matched Sub-Cohort

Characteristics of the individual-matched sub-cohort analysis according to HIV infection status are presented in Table 4-3a. Fifty-three percent of HIV-unspecified individuals were married compared to only 18% of HIV-infected individuals (p=0.004). In the HIV-unspecified group, the median household income was slightly higher ($32,458 vs. $28,945, p=0.14). Both HIV-infected and HIV-unspecified individuals reside mainly within Baltimore City, 68% and 55%, respectively (p=0.26).

The median duration from diagnosis to surgery was greater for HIV-infected patients than HIV-unspecified individuals (72 vs. 40 days; p=0.02; Table 4-3b). HIV-infected patients also experienced longer hospital stays (9 vs. 5 days; p=0.03); a likely consequence of more post-operative complications. Nearly half of HIV-infected patients experienced ≥2 complications compared to HIV-unspecified patients (46% vs. 9%, p<0.001). There were no statistical differences between mean percent predicted forced vital capacity or mean percent predicted forced expiratory volume in one second. Although, mean percent predicted diffusion lung capacity for carbon monoxide (DLCO)

differed by HIV status, data were available on only 55% (12/22) of HIV-infected and 65% (43/66) of HIV-unspecified patients.

There was no difference between HIV-infected and HIV-unspecified groups among those who received adjuvant therapy (Table 4-3b). Seventy-six percent of patients with stage II or greater had progressive disease. Patients with stage I compared to stage II or greater experienced similar post-operative complication rates (data not shown). Importantly, thirty day mortality did not differ between HIV-infected and HIV-unspecified patients (Table 4-3b). Finally, the number of lung cancer-related deaths did not differ between the HIV-infected and HIV-unspecified groups (Table 4-3b).

Individual-matched modeling estimated the adjusted hazard ratios between HIV-infection status and postoperative mortality (Table 4-4). Matched on age, sex, race, histology, stage, surgical procedure, and surgical date, the crude relative hazard of mortality in the HIV-infected patients was increased by 81% compared to HIV-unspecified patients (crude HR=1.81, 95% CI 1.02-3.25;p=0.047). In the adjusted model, HIV-infected patients were associated with a significantly higher hazard of mortality relative to HIV-unspecified patients (aHR=2.31; 95% CI 1.11-4.81; p=0.026). Having ≥2 complications was associated with an adjusted relative hazard of mortality almost 4 times greater than fewer complications (aHR=3.85; 95% CI 1.39-10.68; p=0.009). The cancer-specific survival of the 22 HIV-infected surgical patients differed significantly by CD4 cell count (Figure 4-2). Survival was significantly shorter among individuals with CD4 cell counts below 200 cells/mm^3 (median survival 8.3 vs. 40.0 months; p=0.031). Of the 6 patients with CD4 count <200 cells/mm^3, five died. Four patients died from their lung cancer, and one patient from AIDS-related causes. Four of the six patients with CD4

counts <200 also had cancer progression after surgery. Additionally, median time after surgery to cancer progression was shorter among HIV-infected compared to HIV-unspecified patients (20.4 months vs. not yet reaching 50th percentile, p=0.061). Figure 4-3 describes cumulative probability of cancer progression between HIV-infected and HIV-unspecified surgical patients.

The associations persisted and remained statistically significant in all sensitivity analyses restricting for HAART era (≥1996) for both the entire cohort and matched subcohort.

Discussion

Compared to HIV-unspecified NSCLC patients, HIV-infected NSCLC patients displayed grim postoperative survival rates. Overall and progression-free survival are equally dismal among HIV-infected patients. Even after adjustment for important clinical prognostic indicators, HIV-infected patients exhibited greater mortality. Among HIV-infected patients, immunosuppression at surgery correlates with rapid decline in survival. This finding runs contrary to prior recommendations advocating surgery for HIV-infected NSCLC patients regardless of immune status [16].

Given the strong relationship between extent of disease and survival, it was expected that stage would account for the majority of variance in the model and attenuate the crude hazard ratio of HIV-infected status [7, 22]. However, this was not the case. Instead, after matching and conditioning on stage, the estimate of HIV infection effect increased, indicating that even with similar NSCLC stage, HIV-infected individuals have significantly poorer survival after surgery. To account for stage migration over the

study's 20 years, the surgical year was included in our regression models and matched study design. Nonetheless, the impact of HIV on long-term survival in either the entire analytic population or in the matched sub-cohort analysis remained significant.

Compared to HIV-unspecified patients, HIV-infected individuals underwent surgery a month later after diagnosis. We can only speculate that this difference is indicative of potential barriers to medical care access commonly associated with HIV-infected populations, including low income, lack of medical insurance, HIV-related comorbidities, drug abuse, and even transient residence [23]. Nevertheless, any delay in surgery had no detrimental effect on survival in HIV patients on multivariable analysis.

We show differences in survival between HIV patients by CD4 cell count, corroborating Thurer et al. who found in 4 HIV-positive NSCLC surgical patients, long-term survival in the sole patient with CD4 lymphocytes >200 cells/mm^3 [11]. This value is not completely arbitrary since constitutional symptoms begin in HIV patients with CD4 counts <300 cells/mm^3, serious opportunistic infections occur at CD4 counts <100 cells/mm^3,[11] and from 1992 to 2006 , the Center for Disease Control defined AIDS as CD4 cell counts < 200 cells/mm^3 [24]. In this study, the CD4 cell count was measured as a fixed variable at the closest time prior to surgery. CD4 count can vary markedly within an individual, especially when patients are non-compliant with antiretroviral regimens [25]. Multiple measures of CD4 cell counts or of the nadir CD4 cell counts could reveal persistently low values that may better characterize immunosuppression.

In our study, HIV-infected patients were significantly more likely to develop ≥2 postoperative complications than HIV-unspecified patients. Increased postoperative complications, in general, and postoperative pulmonary complications, in particular, were

associated with decreased pulmonary functional status [26, 27]. Although DLCO might be a relevant factor, we hesitate to make definitive conclusions due to few study patients with DLCO data. HIV-infected patients also showed increased progression to recurrence. This maybe important since it suggests a potential biologic mechanism of NSCLC progression involving immunosuppression [28].

The obvious limitation of 22 HIV-infected surgical patients is the lack of precision inherent in a small sample size precluding strong recommendations. The observed estimates of effect could simply be due to random variability. Second, it was uncommon to test for HIV antibodies during the initial work-up of the general NSCLC patient at our institution. It is plausible that at NSCLC diagnosis, some individuals with sub-clinical HIV-infection could have been misclassified. However, given the thorough nature of clinical assessments of cancer patients at this institution, the probability of missing an HIV-infected individual is low. Lastly, the treatment assignment of HIV infection status is a complex construct of many factors related to health and survival. Thus, the mechanism through which decreased survival is associated with HIV infection is not clearly understood within the context of this study. Notwithstanding, this study utilized a powerful design and analytic methods to improve statistical efficiency and balance between HIV-infected and HIV-unspecified patients. Unmeasured covariates that could account for the effect estimates observed would have to be strongly associated with HIV infection and survival.

Conclusions

In summary, although surgical treatment remains the best option for localized disease, few HIV-infected NSCLC patients present with resectable disease. Despite HIV-infected patients having comparable 30-day mortality rates to HIV-unspecified patients, surgery is associated with more postoperative complications, more rapid progression to disease recurrence and poorer long-term survival rates. Rapid cancer recurrence and poor long-term survival rates seem particularly evident in patients with chronically suppressed immune status, i.e. patients with CD4 counts <200 cells/mm^3. Careful HIV-infected patient selection based on DLCO may improve post-operative complication rates and optimizing immune status prior to surgery may ameliorate long-term cancer survival rates, but due to the small sample size, no definitive recommendations can be made. Future investigations should consider pooled analytic designs as well as prospective measures of HIV immunosuppression and DLCO.

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Table 4-1. Characteristics of NSCLC Patients who Underwent Surgery According to HIV-Infected and HIV-Unspecified Status. (N=2,452)

	HIV-Infected (n=22)		HIV-Unspecified (n=2,430)		
Characteristics	**#**	**%**	**#**	**%**	p value*
Median age, years & IQR	47.5	42 - 55	65	58 - 72	<0.001
Gender					0.019
Male	17	77.3	1,266	52.1	
Female	5	22.7	1,164	47.9	
Race					<0.001
White	8	36.4	1,981	81.5	
Black/Other	14	63.6	449	18.5	
Histology					0.355
Adenocarcinoma	9	40.9	1,153	47.4	
Squamous cell	8	36.4	663	27.3	
Large cell	3	13.6	162	6.7	
NSCLC, nos	2	9.1	184	7.6	
BAC	0	0.0	232	9.6	
Adenosquamous	0	0.0	36	1.4	
Stage					0.766
I	13	59.1	1,278	52.6	
II	3	13.6	408	16.8	
III	5	22.7	456	18.8	
IV	1	4.6	288	11.8	
Smoking status					
Never	0	0.0	275	11.3	0.163
Ever	22	100	2,155	88.7	
Mean Pack-Years Smoked, years and ± S.D.**	42.6	18.5	53.6	32.9	0.012
Procedure					0.677
Lobectomy	19	86.2	1,830	75.3	
Wedge resection	1	4.6	265	10.9	
Pneumonectomy	1	4.6	136	5.6	
Segmentectomy	0	0.0	81	3.3	
Bilobectomy	1	4.6	44	1.8	
Lung resection, nos	0	0.0	74	3.1	
ASA					0.081
1	0	0.0	5	0.2	
2	0	0.0	430	17.7	
3	20	90.9	1,829	75.3	
4	2	9.1	166	6.8	
5	0	0.0	0	0.0	
30-Day Mortality	0	0.0	57	2.3	0.991
Median time from diagnosis to surgery, days & IQR	72	36 - 108	37	18 - 70	0.001

* χ^2 test for homogeneity or Fisher's exact test for binary and categorical variables; nonparametric Mann-Whitney U test or Student's *t*-test for continuous variables.
** Number of pack years smoked on 1,839/2,542 (75%) of patients.
IQR, interquartile range; NSCLC, nos, non-small cell lung cancer, not otherwise specified; BAC, bronchioloalveolar carcinoma; S.D., standard deviation; ASA, American Society of Anesthesiology Classification morbidity index.

Table 4-2. Crude and Multivariable Cox Regression Models of Long-term Survival for NSCLC Patients after Surgery. (N=2,452)

	Crude Hazard Ratio	95% CI	p value	Adjusted Hazard Ratio*	95% CI	p value
HIV infection status						
HIV-Unspecified	1.00	referent		1.00	referent	
HIV-Infected	2.24	(1.37 - 3.68)	0.001	3.08	(1.85 - 5.13)	<0.001

* Adjusted for HIV infection, age, sex, race, NSCLC histology, HAART era (<1996 vs. ≥1996), stage, surgical procedure, ASA classification, smoking status, and days from diagnosis to surgery.

Table 4-3a. Study Characteristics of a Matched Sub-Cohort of NSCLC Surgical Patients According to HIV-Infected and HIV-Unspecified Status. (N=88)

	HIV-Infected (n=22)		HIV-Unspecified† (n=66)		
Characteristics	**#**	**%**	**#**	**%**	p value*
Median age, years & IQR	48	42 - 55	52	46 - 58	0.175
Sex					1.00
Male	17	77.3	51	77.3	
Female	5	22.7	15	22.7	
Race					0.899
White	8	36.4	25	37.9	
Black	14	63.6	41	62.1	
Marital Status					0.004
Not Married	18	81.8	31	47.0	
Married	4	18.2	35	53.0	
Median household income, dollar & IQR	28,945	24,223 - 31,971	32,458	20,465 - 52,973	0.143
Location of residence					0.262
Outside Baltimore City	7	31.8	30	45.5	
Within Baltimore City	15	68.2	36	54.5	
Diagnosis by HAART era					0.752
<1996	3	13.6	12	18.2	
≥1996	19	86.4	54	81.8	
Histology					0.129
Adenocarcinoma	9	40.9	30	45.5	
Squamous cell	8	36.4	20	30.3	
Large cell	3	13.6	1	1.5	
BAC	0	0.0	6	9.1	
NSCLC, nos	2	9.1	9	13.6	
Stage					0.989
I	13	59.1	37	56.1	
II	3	13.6	11	16.7	
III	5	22.7	15	22.7	
IV**	1	4.6	3	4.5	
Smoking Status					0.330
Never	0	0.0	6	9.1	
Former	0	0.0	12	18.2	
Current	22	100	48	72.7	
Mean Pack-Years Smoked, years and ± S.D.	42.6	18.5	45.3	24.7	0.606

† HIV-unspecified patients were matched on age, sex, race, stage, NSCLC histology, date of surgery, and surgical procedure.
* χ^2 test for homogeneity or Fisher's exact test for binary and categorical variables and nonparametric Mann-Whitney U test or Student's *t*-test for continuous variables.

** Metastatic site includes, *HIV-infected*: contralateral lesions with paratracheal nodal involvement (1). *HIV-unspecified*: solitary brain lesion (3).
IQR, interquartile range; NSCLC, nos, non-small cell lung cancer, not otherwise specified; BAC, bronchioloalveolar carcinoma; S.D., standard deviation.

Table 4-3b. Treatment Characteristics of a Matched Sub-Cohort of NSCLC Surgical Patients According to HIV-Infected and HIV-Unspecified Status. (N=88)

	HIV-Infected (n=22)		HIV-Unspecified† (n=66)		
Characteristics	#	%	#	%	p value*
Surgical Procedure					0.903
Lobectomy	19	86.2	51	77.2	
Puemonectomy	1	4.6	6	9.1	
Wedge resection	1	4.6	4	6.1	
Bilobectomy	1	4.6	2	3.0	
Lung resection, nos	0	0.0	3	4.6	
ASA					0.101
2	0	0.0	10	15.2	
3	20	90.9	53	80.3	
4	2	9.1	3	4.5	
Median time from diagnosis to surgery, days & IQR	72	36 - 108	40	15 – 91	0.020
Median length of hospital stay, days and IQR	9	6 -12	5	4 – 7	0.025
Mean number of days until chest tube removal, days and ± S.D	6	3.9	4	2.7	0.068
Neoadjuvant Therapy					0.503
None	54	81.8	20	90.9	
Received	12	18.2	2	9.1	
Adjuvant Therapy					0.367
None	41	62.1	16	72.7	
Received	25	37.9	6	27.2	
Pulmonary Function					
Mean FVC % predicted, ± S.D	87.8	17.3	82.8	18.3	0.314
Mean FEV1 % predicted, ± S.D	80.4	24.9	72.9	19.9	0.262
Mean DLCO % predicted, ± S.D	69.1	20.6	86.1	25.2	0.025
Postoperative Complications§					
Pulmonary	13	59.1	12	18.2	0.001
Cardiac	0	0.0	3	4.5	0.570
Infectious	8	36.4	3	4.5	<0.001
Neurologic	0	0.0	2	3.0	0.899
Bleeding	4	18.2	1	1.5	0.013
Other Complications	6	27.3	2	3.0	0.003
At least two postoperative complications					<0.001
<2	12	54.5	60	90.9	
≥2	10	45.5	6	9.1	
Mean number of days until first complication, days and ± S.D	3	2.4	3	1.9	0.985
30-Day Mortality	0	0.0	1	1.5	0.994
Cause of Death					0.361
Lung cancer-related	11	61.1	27	60.0	
AIDS-related	1	5.6	0	0.0	
Other Causes‡	4	22.2	15	33.3	
Cause Unknown	2	11.1	3	6.7	

† HIV-unspecified patients were matched on age, sex, race, stage, NSCLC histology, surgery date, and surgical procedure.

* χ^2 test for homogeneity or Fisher's exact test for binary and categorical variables and Mann-Whitney U test or Student's *t*-test for continuous variables.

§ Postoperative complications include, ***Pulmonary***: air leak (13), atelectasis (6), pneumothroax (7), pleural effusion (7), pulmonary embolus (3), ARDS (1), respiratory failure (1), hypoxia (1); ***Cardiac***: dysrhythmia (2), myocaridal infarct (1); ***Infectious***: pneumonia (4), fever (4), wound infection (4), bronchiopleural fistula (1), chest infection (1); ***Neurologic***: mental status change (2); ***Bleeding***: thoracic wall hemotoma (1), tracheostomy bleeding (1), persistent hemoptysis (1), chest hemorrage (1); ***Other complications***: acute renal failure (2), reintubation (2), blood clot (1), ileus (1), uncontrolled pain (1), secondary cancer diagnosis (1). Note- some patients had multiple postoperative complications within a broader

categories listed in the table above.

‡ Other causes of death include, **HIV-infected**: bleeding from tracheostomy (oropharyngeal cancer) (1), congestive heart failure/atherosclerotic CVD(1), respiratory failure septic shock ascending cholangitis hepatic artery injury PEA arrest (1), multisystem organ failure following cardiac surgery (1). **HIV-unspecified**: CVD/ myocardial infarction (5), pulmonary arrest (2), pneumonia (1), diabetic complication (1), arteriovenous malformation complications (1), pyriform sinus cancer (1), multiple myeloma (1), esophageal cancer (1), breast cancer (1), head and neck cancer (1).
IQR, interquartile range; S.D., standard deviation; ASA, American Society of Anesthesiology Classification morbidity index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLCO, diffusion capacity of the lung for carbon monoxide.

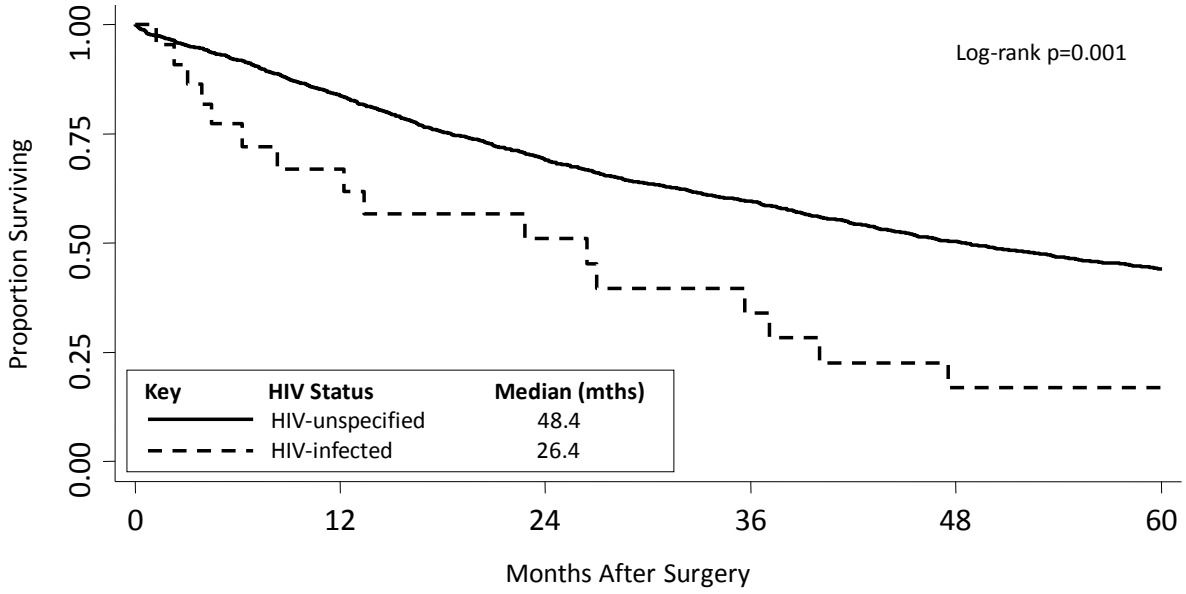
Table 4-4. Crude and Multivariable Cox Regression Models of Long-term Survival for NSCLC Patients after Surgery in a Matched Sub-Cohort. (N=88)

	Crude Hazard Ratio	95% CI	p value	Adjusted Hazard Ratio*	95% CI	p value
HIV infection status						
HIV-Unspecified	1.00	referent		1.00	referent	
HIV-Infected	1.81	(1.02 - 3.25)	0.047	2.31	(1.11 - 4.81)	0.026
Postoperative Complications						
< 2	1.00	referent		1.00	referent	
≥ 2	2.01	(1.03 - 3.92)	0.040	3.85	(1.39 - 10.68)	0.009

***** Adjusted for HIV infection, age, sex, race, marital status, Baltimore City residence, median household income, HAART era (<1996 vs. ≥1996), NSCLC histology, stage, surgical procedure, ASA classification, hospital stay, post-operative complications, smoking status, and days from diagnosis to surgery.

Figure 4-1

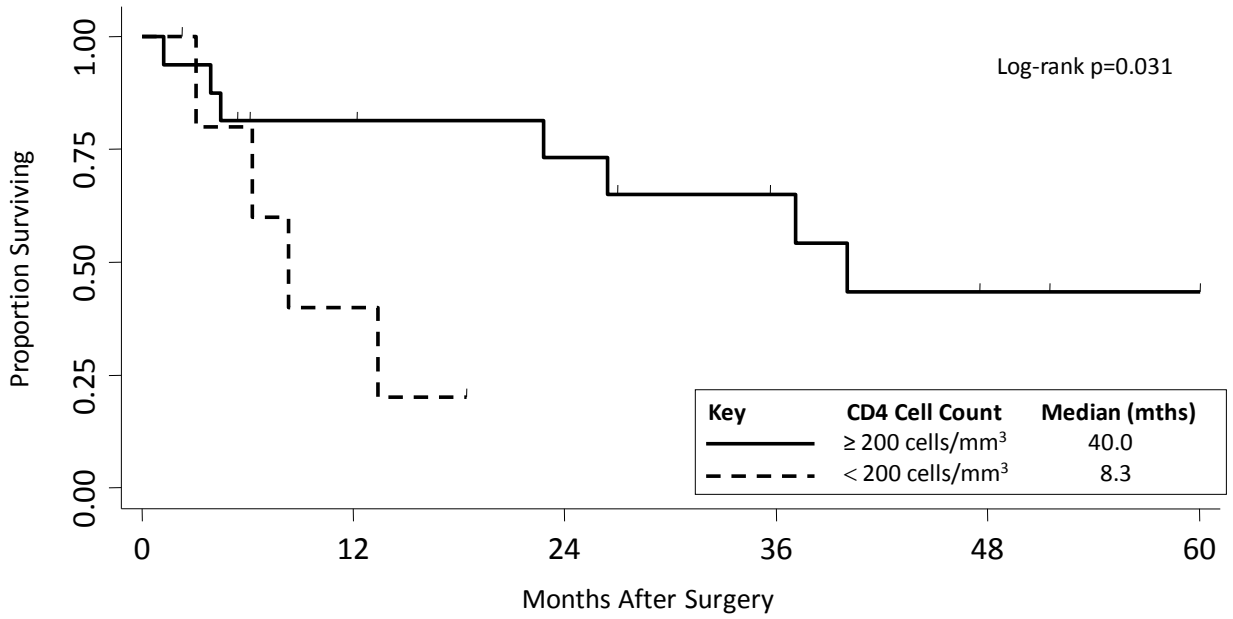
Figure 1. Kaplan-Meier All-Cause Survival Following Surgical Resection Comparing Non-Small Cell Lung Cancer Patients by HIV Infection Status (N=2,452)



No. at Risk (% survived)						
HIV –	2,430 (100)	1,964 (84)	1,493 (69)	1,198 (60)	931 (50)	761 (44)
HIV +	22 (100)	13 (67)	9 (51)	6 (34)	3 (17)	2 (17)

Figure 4-2

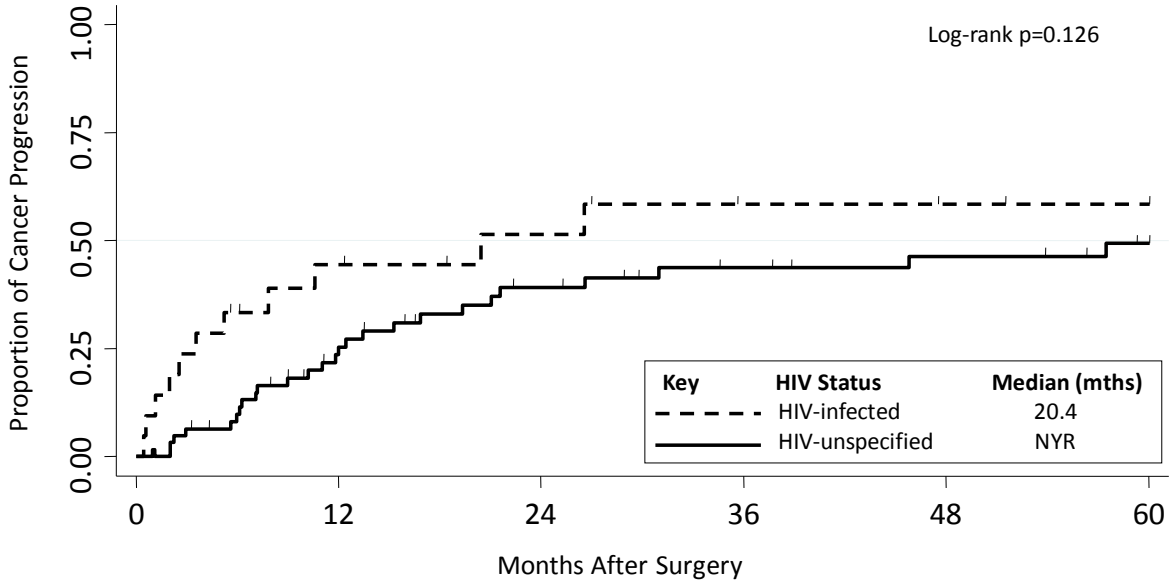
Figure 2. Kaplan-Meier Cancer-Specific Survival of HIV-Infected Non-Small Cell Lung Cancer Patients who Underwent Surgical Resection According to CD4 Cell Count (cells/mm^3) ≥200 vs. <200 (N=22)



No. at Risk (% survived)						
≥200	16 (100)	11 (81)	9 (73)	6 (65)	3 (43)	2 (43)
<200	6 (100)	2 (40)	0 (0)	0 (0)	0 (0)	0 (0)

Figure 4-3

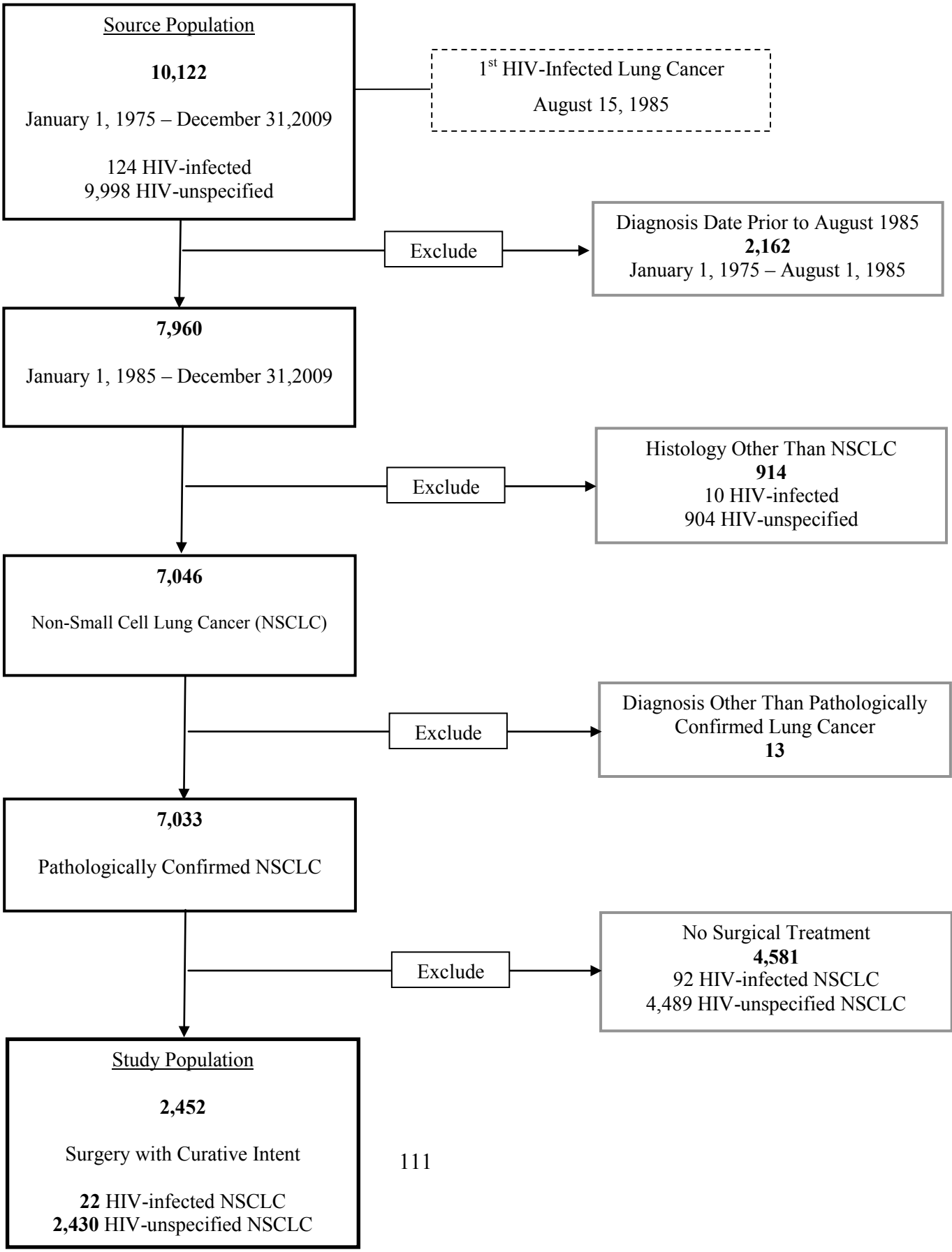
Figure 3. Cumulative Probability of Cancer Progression Following Surgical Resection Comparing Non-Small Cell Lung Cancer Patients by HIV Infection Status (N=84*)



No. at Risk (% progressed)						
HIV +	21 (0)	10 (44)	7 (51)	4 (58)	3 (58)	2 (58)
HIV –	63 (0)	42 (25)	29 (39)	23 (44)	20 (46)	16 (49)

* Stage IV patients excluded (4); NYR, not yet reached.

Appendix 4-1: Exclusions and Inclusions Flow Chart



CHAPTER 5

Conclusions

Synthesis of evidence

The primary objective of this research was to utilize epidemiologic methodologies to identify factors associated with optimal surgical management and examine postoperative outcomes in surgical patients with thoracic cancers within a single hospital setting. We investigated three separate patient populations with distinct but equally important issues related to survival within a clinical setting where surgery was the definitive therapeutic option: 1) locally advanced esophageal cancer patients who received combined neoadjuvant chemoradiation therapy followed by surgery, 2) patients diagnosed with early stage non-small cell lung cancer, and finally 3) HIV-infected patients diagnosed with non-small cell lung cancer. These issues have important implications for future clinical and public health research and impact how decisions are made with respect to treatment and overall survival among patients with thoracic cancer. The three aims and related results are described here.

Aim 1. To assess the long-term postoperative survival of patients with locally advanced esophageal adenocarcinoma treated with combined chemoradiation followed by surgery and adjuvant chemotherapy.

Although current clinical guidelines are becoming more refined results stemming from recent randomized clinical trials with respect to best treatment practices for neoadjuvant chemoradiation and surgery for patient diagnosed with locoregional esophageal cancer, the long-term survival risks and benefits of adjuvant chemotherapy remains unclear. To this point, clinical decision to provide adjuvant chemotherapy is made on a case-by-case basis. The only clinically-based indicator for predicting long-

term survival of patients with locally advanced esophageal cancer is pathological response to neoadjuvant chemoradiation followed by surgery. A pathological complete response confers the best long-term survival for patients with 5-year postoperative overall survival ranging from 50% to 80% compared with pathological partial- and no-response about (35% and 20%, respectively) [1].

We hypothesized that patients diagnosed with locally advanced esophageal adenocarcinoma who received adjuvant chemotherapy would have improved survival compared to patients with similar clinicopathologic characteristics and pathologic response who received combined chemoradiation followed by surgery alone treated at Johns Hopkins Hospital from 1989 to 2011. In this single-institution, retrospective cohort study spanning more than 20 years, we found that patients who received adjuvant chemotherapy had a decrease in relative hazards for postoperative mortality compared to patients who did not receive adjuvant chemotherapy, after adjusting for age, ASA performance status, and pathologic complete response. In addition, when stratified by pathologic response, partial responders were found to have the most survival benefit from adjuvant chemotherapy with longer median survival vs. partial responders that received multimodality therapy alone. Our data suggest that when a neoadjuvant chemotherapy regimen that induces a significant pathologic response, more of that same chemotherapy given adjuvantly may increase survival benefit. Conversely, if the neoadjuvant chemotherapy regimen does not provoke a significant pathologic response, changing the adjuvant therapy to a different chemotherapeutic regimen may improve survival among pathologic partial responders.

Results from this study may aid clinicians in deciding whether patients with pathologic complete, partial, or no response to multimodality therapy should continue treatment with adjuvant chemotherapy. Finally, this study marks the initial movement toward a better understanding of a continuum of therapy for locally advanced esophageal cancer patients from neoadjuvant chemoradiation to surgery and potentially to subsequent adjuvant chemotherapy. It is our hope that findings from this study will serve as a basis of constructive dialogue for which to improve upon methodology and scope for future large-scale prospective studies leading to more definitive randomized control trials.

Aim 2. To examine differences by race on recommendation for surgical therapy and postoperative survival among early stage non-small cell lung cancer patients.

Given the striking difference in survival between patients with early stage non-small cell lung cancer who undergo surgical resection and those who have alternative treatment, it is not surprising that research has shown that much of the higher mortality in blacks with early stage NSCLC can be attributed to lower surgical rates compared with whites [2]. However, it has been difficult to directly assess the underlying reason for this disparity in surgical rates. To better understand the factors influencing the recommendation for surgery, we conducted a retrospective cohort study with early stage NSCLC patients treated at Johns Hopkins Hospital from 2000 to 2010.

We hypothesized that there would be no racial disparities among patients with early-stage non-small cell lung cancer patients who received a recommendation for surgery at Johns Hopkins Hospital between 2000 and 2010. We further hypothesized that overall survival would not differ by race once surgical recommendation was taken into

account. Results for this study showed that black patients were recommended for surgery 8% less than white patients, but after accounting for patient-, tumor-, and physician-related factors no association existed by race. Race as a risk factor alone was not independently associated with surgical recommendation or overall survival. Our findings suggest that patient-, tumor-, and physician-related factors have a greater influence in the treatment recommendation decision process than race alone. Access to care with respect to consultation for surgical treatment did not differ by race. Furthermore, among patients whose initial physician encounter was with a non-surgeon, if the recommendation was not to have surgery a surgeon consequently corroborated the recommendation equally by race.

Aim 3. To determine the effect of HIV infection on post-surgical outcomes among non-small cell lung cancer patients.

At present, the general consensus based on limited information the recommendations for surgical intervention for HIV-infected individuals remain similar to general lung cancer population, namely surgical resection for curative intent in HIV-infected patients with localized disease and good performance status [3]. We hypothesized that HIV-infected patients with NSCLC would have poorer postoperative survival compared to HIV-unspecified NSCLC patients with similar clinical risk factors who underwent surgery at Johns Hopkins Hospital from 1985 to 2009. We further hypothesized that HIV-infected patients would have shorter time to disease progression as compared to HIV-unspecified patients with similar clinical risk factors following surgery with curative intent.

The analysis in this study compared HIV-infected NSCLC surgical patients to all HIV-unspecified NSCLC patients that received surgery during the same time period (unmatched) and then a 3:1 individual matched sub-group analysis to examine more detailed surgical characteristics. Results from both analyses conferred dismal prognosis for HIV-infected NSCLC patients. Compared to HIV-unspecified NSCLC patients, postoperative overall survival and progression-free survival was significantly shorter in HIV-infected NSCLC patients. Even after matching on major clinical prognostic factors, HIV-infected patients exhibited a greater relative hazard for mortality. Within the HIV-infected NSCLC group, patients with a CD4 count $\leq$200 cells/mm^3 at time of surgery had significantly poorer survival. Additionally, following surgery, HIV-infected NSCLC patients developed more postoperative complications and showed more rapid progression to metastatic disease or recurrence compared to HIV-unspecified NSCLC patients.

Although surgical treatment remains the best option for localized NSCLC, results from this study suggest HIV-infected NSCLC have poorer survival and disease-free survival after surgery as compared to the general lung cancer population. These observations may be explained in part by inadequate recovery after surgery and more aggressive disease progression due to chronic immunosuppression or more aggressive tumor biology. Clinical decisions for surgical management among HIV-infected patients diagnosed with NSCLC should consider the patient's overall health status and encourage initiation or continuation of highly active antiretroviral therapy.

Clinical significance

This research contributes important information for medical decision-making between clinicians and patients considering best surgical management practices for patients with esophageal and lung cancer. First, we found in esophageal adenocarcinoma patients, specifically pathologic partial responders, that adjuvant therapy can provide improved postoperative survival. Furthermore, patients that had a significant clinical response to a specific neoadjuvant chemotherapy regimen and continued to receive the same adjuvant chemotherapy regimen had better median postoperative survival compared to patients that received a different adjuvant chemotherapy regimen. The two most frequently administered classes of chemotherapy are platinum- and taxane-based chemotherapies. There are no clinical or molecular markers to help guide clinicians decisions on how to predict patient response to a specific neoadjuvant chemotherapeutic regimen. Although patients in our study were not explicitly randomized to a particular neoadjuvant chemotherapy regimen, results from our study may help to reinforce clinical decisions on adjuvant chemotherapeutic regimens.

Public health significance

Several areas of research stemming from these studies have important implications beyond the clinical setting. Mainly, race and ethnic disparities in the receipt of treatment for lung cancer is an important public health concern. Racial and ethnic minority and white patients who receive similar care for the same stage of disease have been shown to have similar survival for lung cancer, irrespective of socioeconomic status [4, 5]. New data on CT screening for lung cancer suggest a 20% reduction in mortality for persons at

high risk [6]. In fact, the 2013 American College of Chest Physicians (ACCP) Lung Cancer Guidelines (LC III) suggests, "*3.4.1. For smokers and former smokers who are age 55 to 74 and who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low-dose CT (LDCT) should be offered over both annual screening with CXR or no screening, but only in settings that can deliver the comprehensive care provided to National Lung Screening Trial participants (Grade 2B).*" [7].

Early diagnosis of lung cancer provides the best chance for optimal treatment for cure. Results from our study support the conclusion that surgery at early stage provides equal opportunity for improved overall survival, irrespective of race and socioeconomic status. Public health interventions that emphasize improved access to CT screening for lung cancer and subsequent early treatment across race and socioeconomic status will likely play a critical role in the reduction of lung cancer deaths. Finally, these studies add to the evidence base for future research on surgical management and postoperative outcomes for patients with thoracic cancer.

Future research directions

Findings from this research suggest several future lines of investigation. Currently, clinicians still rely on histopathological examination of the resected specimen to determine the degree of pathologic response to neoadjuvant therapy. Our research group has begun investigating markers to predict pathological response to neoadjuvant therapy. As we have found, patients undergoing neoadjuvant therapy who are deemed non-responders fared worse in survival, stage for stage, than all other treatment groups.

Identifying this subgroup of patients with esophageal cancer would potentially avoid neoadjuvant therapy in about 20% of patients who would not benefit from such an approach. This would allow for surgical treatment or potential alternative regimens to be initiated earlier. Genetic analysis of esophageal cancer and its histological sub-types, adenocarcinoma and squamous cell carcinoma, may offer a new strategy of improved outcomes through detection of molecular biomarkers. Prognostic stratification of patients will promote the development of new targeted therapies leading to better response rates and lower treatment-related morbidity.

A particularly promising novel biomarker is emerging as a predictor to taxane-based chemotherapy [8]. *Checkpoint with FHA and ring finger domains* (CHFR) is a mitotic checkpoint- and tumor suppressor gene and is inactivated in a diverse number of solid malignancies [8]. CHFR inactivation has been identified in studies as a prognostic marker for reduced outcomes for NSCLC [9, 10] and colorectal cancer [11]. CHFR also has been identified as a predictive marker to increased sensitivity to taxane-based chemotherapeutic agents for NSCLC [12, 13], gastric [14], cervical [15], and endometrial cancers [16]. Taxane-based chemotherapeutic agents, along with platinum-based chemotherapies, are mainstay treatments for both NSCLC [17] and esophageal cancer [18] .

Our research group is currently enrolling locally advanced esophageal adenocarcinoma patients into a phase II trial at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins investigating CHFR methlyation status on pathologic response to neoadjuvant chemotherapy and radiation comparing taxane- and platinum-based regimens (paclitaxel and cisplatin, respectively) compared to platinum-based

regimens alone followed by surgery [19]. The objective of this study is to determine the rate of pathological complete response when the inclusion of paclitaxel chemotherapy regimen in neoadjuvant therapy is based on the presence or absence of CHFR methylation in diagnostic biopsy specimens. While this is not a randomized clinical trial, we hope to gain further knowledge on how molecular biomarker analysis can help to inform clinicians on better treatment options for esophageal cancer patients.

We found that access to surgery, at our institution, did not differ between black and white patients with early stage NSCLC. Health disparities research on treatment for lung cancer remains complex and evidence demonstrates that no one factor can be fully attributed to treatment inequalities. The complex interaction between race, socioeconomic status, and other socio-cultural mechanisms may overshadow more proximal determinants of treatment. Perhaps we should try to better understand and appreciate the influence of more specific social or economically influenced barriers to cancer treatment, such as availability for care, (i.e., the ability to take time off work, lack of support for child/spousal care), transportation to medical appointments, support systems, and attitudes and understanding of disease severity. Studies that can examine more personal influenced barriers to cancer treatment may prove more informative for the development of interventions designed to reduce health disparities.

Studies have shown that age-adjusted incidence of lung cancer is greater among HIV-infected individuals compared to the general lung cancer population [20, 21]. It is unclear whether the elevated increase in risk for lung cancer among HIV-infected patients is due to excessive cigarette smoking prevalence or factors directly related to the HIV disease and/or its associated co-morbidities and treatment. Regardless of the risk factors,

lung cancer has become a leading cause of death among HIV-infected persons [22]. The majority of HIV-infected patients are diagnosed with advanced stage lung cancer, when palliative chemotherapy and radiation therapy are the only available treatment options however there is a paucity of data on the treatment effects and chemo- and radiation-toxicity of systemic therapy in this population.

An important bioethical debate with public health policy implications has focused on the exclusion of HIV-infected persons from cancer clinical trials. A review of the NCI's Physician Data Query (PDQ) clinical trial database revealed that approximately 25% (95 of 383) phase I, II, and III treatment trials for non-small cell lung cancer explicitly exclude HIV infection [23]. Problems with excluding HIV-infected individuals from cancer clinical and screening trials can limit the representativeness of the study sample, thus reducing generalizability, and potentially limit the evidence base for cancer therapy. Improvements in HIV treatment and survival have consequently allowed for advances in treatment of certain AIDS-defining cancers, which have resulted in outcomes equivalent to those seen in similar cancers in the HIV-seronegative population [24]. Future trial designs must place emphasis on fair evaluation of cancer patients with HIV infection for reasonable and safe access to cancer clinical trials and potentially clinically promising therapies.

The National Lung Cancer CT screening Trial (NLST) reported a 20% reduction in mortality associated with annual computed tomography (CT) screening for older, heavy smokers at high risk for lung cancer [6]. Given that the majority of HIV-associated lung cancers are diagnosed at late stage, CT screening may have profound implications for improving earlier diagnosis of this high-risk group. There are no data, however, to

support routine lung cancer screening in HIV-infected smokers because most CT screening studies, including the NLST, excluded their enrollment. For the same reasons as cancer clinical trials, fair recruitment into future CT screening trials should be considered for HIV-infected smokers at high risk for lung cancer.

Conclusions

This dissertation used clinical epidemiological methodologies to examine outcomes associated with optimal surgical management for lung and esophageal cancer patients treated at Johns Hopkins Hospital. We have found that adjuvant chemotherapy was associated with a reduction in mortality for esophageal adenocarcinoma patients after neoadjuvant chemoradiation followed by surgery. Pathologic partial responders have the most benefit to adjuvant chemotherapy compared to pathologic complete and non-responders. Future research on molecular biomarkers that can predict pathologic response to neoadjuvant therapy will help improve clinical decisions, reduce potential harm due to unnecessary additional therapy, and advance research for individualized therapies.

We contributed to the body of evidence on racial and ethnic disparities in surgical treatment patients diagnosed with early stage NSCLC. Conclusions from our investigation on race disparities in surgical recommendation suggest that race alone was not an independent risk factor for surgical recommendation or survival after accounting for patient-, tumor-, and physician-related factors. Racial disparities in surgical resection rates might be explained, in part, by social and economic conditions specific to the patient. On a clinical level, future research designs should focus on patient-level factors for example, time off work to undergo treatment, lack of social and spousal support, need

to care for another family sick member, transportation to medical visits, and awareness of disease severity. Information about specific patient-level factors that can help clinicians identify candidates for surgery with curative intent at high risk for refusing surgery realistically can only be accomplished within a clinical setting. Nevertheless, public health efforts must continue to improve minority inclusion into CT screening, clinical trials, and primary prevention programs on a population level.

Finally, we observed HIV-infected NSCLC patients to be associated with shorter postoperative survival compared to HIV-unspecified NSCLC patients with similar clinical characteristics. Surgical resection remains the best treatment for cure for NSCLC however HIV-infected NSCLC patients have more postoperative complications and rapid progression of disease after surgery. Clinicians should consider the overall health status and immune function of NSCLC patients with HIV infection before surgery and also consider adjuvant chemotherapy with extra vigilance following surgery.

Future research is necessary to further understand the relationships studied in each aim of this dissertation. Furthermore, efforts need to be made by both the medical and public health community to promote the policy, prevention, early detection, and treatment of thoracic cancers.

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The Johns Hopkins University
Bloomberg School of Public Health
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Department of Epidemiology
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Bloomberg School of Public Health
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Department of Epidemiology
Masters of Public Health, May 2002

Virginia Polytechnic Institute and State University
Virginia Tech, Blacksburg, Virginia
Department of Psychology, Department of Statistics
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Professional Experience:

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-Implement national multicenter thoracic surgical database
-Supervise program manager and research support staff
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The Johns Hopkins University, School of Medicine
Department of Oncology, Division of Cancer Biology, Baltimore, MD
Faculty, *Research Associate, October 2002 – December 2012*
Supervisors: Malcolm V. Brock, M.D. and Stephen Baylin, M.D.
-Identified novel research questions meaningful to clinical, molecular, and epigenetic cancer.
-Designed and conducted epidemiological, clinical, and translational studies.
-Performed, interpreted and reported complex statistical analyses.
-Consulted on epidemiologic methodology and study design.
-Managed large institutional lung and esophageal cancer databases.

Graduate (MPH Program):

The Johns Hopkins University, Bloomberg School of Public Health
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The Johns Hopkins University, School of Medicine
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Supervisor: James Zabora, Sc.D.

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Journal Publications:

* Denotes equal contribution as first author.

43. Shah SP, Xu T, **Hooker CM**, Hulbert A, Battfarano RJ, Brock MV, Mungo B, Molena D, Yang SC. Why are patients being readmitted after surgery for esophageal cancer? *J Thorac Cardiovasc Surg*. 2014 [*submission under peer review*].

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30. Juergens RA, Wrangle J, Vendetti FP, Murphy SC, Zhao M, Coleman B, Sebree R, Rodgers K, **Hooker CM**, Franco N, Lee B, Tsai S, Delgado IE, Rudek MA, Belinsky SA, Herman JG, Baylin SB, Brock MV, Rudin CM. Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. *Cancer Discovery*. 2011 Dec;1(7):598-607.

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20. Licchesi, J, Westra WH, **Hooker CM**, Herman JG. Promoter hypermethylation of hallmark cancer genes in atypical adenomatous hyperplasia of the lung. *Clin Cancer Res*. 2008 May; 14(9):2570-8.

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elevated mortality in an urban population with HIV and lung cancer: Implications for patient care. *J Aquir Immune Defic Syndr*. 2006 Sep; 43(1):47-55.

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12. Brock MV*, **Hooker CM***, Syphard JE, Westra W, Xu L, Alberg AJ, Mason D, Baylin SB, Herman JG, Yung RC, Brahmer J, Rudin CM, Ettinger DS, Yang SC. Surgical resection of limited disease small cell lung cancer in the new ear of platinum chemotherapy: Its time has come. *J Thoracic Card Surg.* 2005 Jan; 129(1):64-72.

11. Mingzhou G, Yoshimitsu A, House MG, **Hooker CM**, Heath E, Gabrielson E, Yang SC, Han Y, Baylin SB, Herman JG, Brock MV. Hypermethylation of the GATA genes in lung cancer. *Clin Cancer Res.* 2004 Dec; 10(23):7917-24.

10. Mingzhuo G, House MG, **Hooker CM**, Han Y, Heath E, Gabrielson E, Yang SC, Baylin SB, Herman JG, Brock MV. Promoter hypermethylation of resected bronchial margins: A field defect of changes? *Clin Cancer Res*. 2004 Aug; 10(15):5131-36.

9. Brock MV, Alberg AJ, **Hooker CM**, Kammer AL, Xu L, Roig CM, Yang S. "Risk of subsequent primary neoplasms developing in lung cancer patients with prior malignancies." *J Thoracic Card Surg*. 2004 Mar; 127(4):1119-25.

8. Brock MV, Kim MP, **Hooker CM**, Alberg AJ, Jordan M, Roig CM, Xu L, Yang SC. "Pulmonary resection in octogenarians with stage I non-small cell lung cancer: A 22-year experience." *Ann Thoracic Surg.* 2004 Jan; 77(1):271-7.

7. House MG, Guo MZ, Efron DT, Lillemoe KD, Cameron JL, Syphard JE, **Hooker CM**, Abraham SC, Elizabeth CM, Montgomery A, Herman JG, Brock MV. "Tumor suppressor gene methylation as a predictor of gastric stromal tumor behavior." *J Gastrointest Surgery*. 2003 Dec; 7(8):1004-1014

6. House MG, Herman JG, Guo MZ, Schulick RD, **Hooker CM**, Lillemoe KD, Cameron JL, Hruban RH, Maitra A, Yeo CJ. "Prognostic value of hMLH1 hypermethylation and microsatellite instability in surgically resected endocrine tumors of the pancreas." *Surgery*. 2003 Dec; 134(6):902-8.

5. Spagnola S, Zabora J, BrintzenhofeSzoc K, **Hooker CM**, Cohen G, Baker F. "The satisfaction with life domains scale for breast cancer (SLDS-BC)." *Breast J*. 2003 Nov; 9(6):463-71.

4. House MG, Herman JG, Guo MZ, **Hooker CM**, Schulick RD, Lillemoe KD, Cameron JL, Hruban RH, Maitra A, Yeo CJ. "Aberrant hypermethylation of tumor suppressor genes in pancreatic neuroendocrine neoplasms." *Ann Surg*. 2003 Sep; 238(3):423-31; discussion 431-2.

3. Zabora JR, BrintzenhofeSzoc K, Curbow B, **Hooker CM**, Piantadosi S. "The prevalence of psychological distress by cancer site." *Psycho-Oncology.* 2001; 10:19-28.

2. Zabora JR, BrintzenhofeSzoc K, Curbow B, Piantadosi S, **Hooker CM**, Owens A, Derogatis L. "A new psychosocial instrument for use with cancer patients." *Psychosomatic.,*2001;42:241-6.

1. Bucher JA, Loscalzo M, Zabora JR, Houts P, **Hooker CM**, BrintzenhofeSzoc K. "Problem-solving cancer care education for patients and caregivers." *Cancer Practice.* 2001; 9:66-70.

Presentations:

(Listed presentations within the past ten years)

2014 "Is survival after adjuvant chemotherapy associated with clinical response to tri-modal therapy for esophageal adenocarcinoma?"
10th Annual Cancer Epidemiology, Prevention, and Control Symposium.
Bloomberg School of Public Health, Baltimore, MD

"Why are patients being readmitted after surgery for esophageal cancer?'
94th American Association for Thoracic Surgery Annual Meeting
Toronto, Ontario, Canada

"Clinical Response to Neoadjuvant Therapy to Predict Success of Adjuvant Chemotherapy for Esophageal Adenocarcinoma"
American Society of Clinical Oncology- GI Cancers Symposium
San Francisco, CA

2013 "Minority Status as a Determinant of Tobacco-Caused Health Inequalities: A Global View"
IASLC: 15th World Conference on Lung Cancer
Sydney, Australia

"Has PET Imaging Decreased the Rate of Lung Resection for Benign Solitary Pulmonary Nodules?"
93rd American Association for Thoracic Surgery Annual Meeting

Minneapolis, MN

"Survivorship after Surgical Resection for Cancer: The Need for Continued Surgical Follow-up"
93rd American Association for Thoracic Surgery Annual Meeting
Minneapolis, MN

"Advanced Pulmonary Carcinoid (APC): 20-Year Experience at Johns Hopkins"
American Society of Clinical Oncology Annual Meeting
Chicago, IL

2012 "The Surgery Delay Continuum for Curative Lung Cancer"
5th AACR Conference- The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved
San Diego, CA

"Racial Differences in the Receipt of Optimal Surgical Care and Postoperative Survival among Lung Cancer Patients at a Large Metropolitan Cancer Center.
8th Annual Cancer Epidemiology, Prevention and Control Symposium
Bloomberg School of Public Health, Baltimore, MD

"Estrogen Effect on Esophageal Cancer Incidence"
American Society of Clinical Oncology Annual Meeting
Chicago, IL

"Esophageal Cancer Incidence Gender Disparity"
Society of Black Academic Surgeons Scientific Symposium
Baltimore, MD

"The Surgery Delay Continuum for Curative Lung Cancer"
Society of Black Academic Surgeons Scientific Symposium
Baltimore, MD

2011 "The Importance of the Low Dosage Effect of Azacitidine on H838 Lung Adenocarinoma Tumorigenesis in NOD/SCID mice: A Possible Paradigm Shift in Chemotherapy?"
Society for Thoracic Surgeons
San Francisco, CA

"Preliminary Results from an Urban Patient Cohort, who are at High Risk for Lung Cancer, Excluded from the U.S. National Lung Cancer Screening Trial-Heavy Smokers with HIV."
American Association for Cancer Research Annual Meeting
Orlando, FL

2010 "Neoadjuvant Chemoradiation Therapy for Clinical Stage T2N0 Esophageal Cancer Patients: To Give or Not to Give"
Southern Thoracic Surgical Association 57th Annual Conference
Orlando, FL

"Differences in Survival for Esophageal Cancer Patients who Received Chemoradiation and Surgery"
6th Annual Cancer Epidemiology, Prevention and Control Symposium
Baltimore, MD

2009 "Investigating HIV-Infection as a Risk Factor for Post-Operative Mortality among Non-Small Cell Lung Cancer Patients."
5th Annual Cancer Epidemiology, Prevention and Control Symposium
Bloomberg School of Public Health, Baltimore, MD

2008 "Differences in Promoter Methylation of Tumor Suppressor Genes in Cytogenetically Normal and Abnormal Acute Myeloid Leukemias"
American Society of Hematology
San Francisco, CA

"Failure after Neoadjuvant Chemoradiation and Surgery for Esophageal Cancer: Do Complete Responders Recur Differently than Non-Complete Responders."
Western Thoracic Surgical Association
Kona, HI

"Long-term Survival after Neoadjuvant Chemoradiation and Surgery for Esophageal Cancer: An Institutional Experience."
Surgical Research Forum
Department of Surgery, Johns Hopkins University School of Medicine
"Outcomes of Elderly Patients with Esophageal Cancer: Who Undergoes Esophagectomy?"
Journal of the American College of Surgeons

2007 "Socio-economic Status and Social Isolation as a Determinant of Survival in Non-Small Cell Lung Cancer"
American Association for Cancer Research- Science of Heatlh Disparities Conference
Atlanta, GA

"Screening for Lung Cancer with Molecular Markers: Which Specimen Source is Best?"
George D. Zuidema Surgical Research Symposium
Johns Hopkins University, School of Medicine, Baltimore, MD
"Surgical Outcomes in Non-Smoking Lung Cancer Patients"
Western Thoracic Surgical Association
Santa Ana Pueblo, NM

2006 "Clinical and Molecular Ealuation of Patients with Esophageal Adenocarcinoma from the United States and Japan."
American Society of Clinical Oncology
Atlanta, GA

"Esophageal Adenocarcinoma in African-Americans: Rare and Deadly."
Society of Black Academic Surgeons Scientific Symposium
Cincinnati, OH

"Delayed Diagnosis and Elevated Mortality in an Urban Population with HIV and Lung Cancer: Implications for Patient Care."
SPORE Winter Meeting
Los Angeles, CA

2005 "The Risk of Developing Rectal Cancer Due to Active Smoking and Passive Smoke Exposure."
American College of Epidemiology
New Orleans, LA

"HIV and Lung Cancer Patients: Why Such Poor Survival?"
International Association for the Study of Lung Cancer
Barcelona, Spain

"Pathologic Downstaging with Taxane-Based Neoadjuvant Chemotherapy Correlates with Increased Survival in Patients with Locally Advanced Esophageal Cancer."
American Society for Clinical Oncology
Orlando, FL

"Lung Cancer in Patients with Human Immunodeficiency Virus"
17th Annual B. Frank Polk HIV Research Symposium
Baltimore, MD

"Lung Cancer in Patients 40 Years of Age and Younger: Is Smoking a Factor?"
Society of Black Academic Surgeons Scientific Symposium
Pittsburgh, PA

"Human immunodeficiency virus and lung cancer: Differences in presentation and clinical course."
American Association for Cancer Research Annual Meeting
Anaheim, CA

"Elevated Lung Cancer Incidence in an Urban Cohort of HIV-Infected Individuals."
Conference on Retroviruses and Opportunistic Infections

Chicago, IL

"Can We Improve the Cytological Examination of Malignant Pleural Effusions Using Molecular Analysis?"
Society of Thoracic Surgeons
Tampa, FL

2004 "Surgical Resection Plus Adjuvant Therapy as a Means of Maximizing Local Control in Limited Disease Small Cell Lung Cancer."
Third International Chicago Symposium on Malignancies of the Chest and Head & Neck
Chicago, IL

"Assessing Prognosis in HIV-Positive Lung Cancer Patients."
Pathobiology of Cancer Educational Workshop
American Association For Cancer Research
Snowmass, Colorado

"Lung Cancer as a Common Non-AIDS-related Malignancy: A Report from a Single Institution."
SPORE Summer Meeting
Baltimore, MD

"Hypermethylation of the GATA Gene Family in Lung Cancer."
Society of Black Academic Surgeons
Washington, DC

"Promoter Hypermethylation of Resected Bronchial Margins: Implications for Lung Cancer Recurrence?"
American Association For Cancer Research
Orlando, FL

"HIV Infection and Lung Cancer: A Poor Prognostic Factor?"
SPORE Winter Meeting
St. Petersburg, FL

"Surgical Resection of Limited Disease Small Cell Lung Cancer in the New Era of Platinum Chemotherapy: Its Time Has Come."
American Association for Thoracic Surgery
Toronto, Ontario, Canada

"Esophageal Adenocarcinoma in African-Americans: A Clinicopathological Variant of Esophageal Cancer?"
American Association for Thoracic Surgery
Toronto, Ontario, Canada

2003 "Are Multiple Tumors in Lung Cancer Patients Primarily Due to Tobacco?"
American Association of Cancer Research
Washington, DC

"Risk of Subsequent Primary Neoplasms Developing in Lung Cancer Patients with Prior Malignancies."
American Association for Thoracic Surgery
Boston, MA

"Pulmonary Resection in the Octogenarian with Stage I Non-Small Cell Lung Cancer (NSCLC): A 22 Year Experience."
Society of Thoracic Surgeons
San Diego, CA

"Prognostic Value of hMLH1 Hypermethylation and Microsatellite Instability in Surgically Resected Endocrine Tumors of the Pancreas."
American Association of Endocrine Surgeons
San Diego, CA

"Tumor Suppressor Gene Hypermethylation as a Predictor of Gastric Stromal Tumor Behavior."
Society of Surgery of the Alimentary Tract, Digestive Disease Week
Orlando, FL

* Presentations and abstracts prior to 2002 are available upon request.

Editorial Activities:

Reviewer:
Molecular Cancer Therapeutics, 2013 – present
Journal of Surgical Research, 2013 – present

Educational Activities:

Teaching

2011 Graduate Teaching Assistant
Epidemiologic Methods, Section I of IV
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
2010 Graduate Teaching Assistant
Epidemiologic Methods, Section II of IV
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Mentoring

Undergraduate Students:

Benjamin Cooper; JHU, Honors thesis advisor
Hayley Osen; JHU, Honors thesis advisoru
Johnathon Taylor; JHU, Honors thesis advisor
Nicholas Theodosakis, UVA, Honors thesis advisor
Aliyah Sanders; JHU, Honors thesis advisor

Medical Students:

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Nan Zhu; JHU, 2008 AATS Surgical Fellowship recipient, mentor
Joshua Taylor; JHU, Surgical research, advisor
Helen Selonick-Prevas, JHU, Medical oncology research, advisor
Yelena Prints; JHU, Medical oncology research, advisor
Joani Christensen; JHU, Medical oncology research, advisor
Nance Yuan; JHU, Medical oncology research, advisor
Solange Cox; JHU, Surgical research, advisor
Jennifer Zhang; JHU, 2010 AATS Surgical Fellowship recipient, mentor
George Yufei Tang; JHU, 2011 AATS Surgical Fellowship recipient, mentor
Kanika Trehan; JHU, Surgical research, advisor
Vernissia Tam; JHU, Surgical research, advisor
Malcolm Stennet; Howard University, 2013 AATS Surgical Fellowship recipient, mentor
Tim Xu; JHU, Surgical research, advisor
Sneha Shah; JHU, Surgical research, advisor
Jessica Moore; JHU, 2014 AATS Surgical Fellowship recipient, mentor

Medical/Surgical Fellows:

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Luckson Mathieu, M.D.; JHU, general clinical outcomes and epidemiology research
John Wrangle, M.D., M.P.H; JHU, general clinical outcomes research
Mario Teran, M.D.; JHU, surgical outcomes research

Honors and Awards:

2009 Harvey M. Meyerhoff Fellowship in Cancer Prevention
The Johns Hopkins Bloomberg School of Public Health
2004 The Edward A. Smuckler Memorial Workshop: Pathobiology of Cancer Scholarship Educational Workshop
American Association For Cancer Research
2002 Trish Greene Quality of Life Award
American Cancer Society

Affiliations:

American Association for Cancer Research
Associate member, July 2004 - Present
Society of Thoracic Surgeons
Associate member, June 2013 - Present
Society of Epidemiologic Research

Certifications:

2011 CITI- Human Subjects Research Ethics Certification
Johns Hopkins Bloomberg School of Public Health
2003 HIPAA Compliance Training Certification
The Johns Hopkins University School of Medicine
1999 Human Subjects Research Compliance Certification
The Johns Hopkins University School of Medicine

Technical Experience:

Proficient in the following statistical packages:
- STATA, R, SAS